Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: interventional study

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Abstract

Objective: To assess the response of healthy infants to airway hypoxia (15% oxygen in nitrogen).
Design: Interventional study.
Settings: Infants' homes and paediatric ward.
Subjects: 34 healthy infants (20 boys) born at term; mean age at study 3.1 months. 13 of the infants had siblings whose deaths had been ascribed to the sudden infant death syndrome.
Intervention: Respiratory variables were measured in room air (pre-challenge), while infants were exposed to 15% oxygen (challenge), and after infants were returned to room air (post-challenge).
Main outcome measures: Baseline oxygen saturation as measured by pulse oximetry, frequency of isolated and periodic apnoea, and frequency of desaturation (oxygen saturation ≤80% for ≥4 s). Exposure to 15% oxygen was terminated if oxygen saturation fell to ≤80% for ≥1 min.
Results: Mean duration of exposure to 15% oxygen was 6.3 (SD 2.9) hours. Baseline oxygen saturation fell from a median of 97.6% (range 94.0% to 100%) in room air to 92.8% (84.7% to 100%) in 15% oxygen. There was no correlation between baseline oxygen saturation in room air and the extent of the fall in baseline oxygen saturation on exposure to 15% oxygen. During exposure to 15% oxygen there was a reduction in the proportion of time spent in regular breathing pattern and a 3.5-fold increase in the proportion of time spent in periodic apnoea ($P < 0.001$). There was an increase in the frequency of desaturation from 0 episodes per hour (range 0 to 0.2) to 0.4 episodes per hour (0 to 35) ($P < 0.001$). In 4 infants exposure to hypoxic conditions was ended early because of prolonged and severe falls in oxygen saturation.
Conclusions: A proportion of infants had episodes of prolonged (≤80% for ≥1 min) or recurrent shorter (≤80% for ≥4 s) desaturation, or both, when exposed to airway hypoxia. The quality and quantity of this response was unpredictable. These findings may explain why some infants with airway hypoxia caused by respiratory infection develop more severe hypoxaemia than others. Exposure to airway hypoxia similar to that experienced during air travel or on holiday at high altitude may be harmful to some infants.

Introduction

A reduction in the partial pressure of inspired oxygen may increase the risk of apparent life threatening events and sudden death in infancy.[1–4] Airway hypoxia can be caused by respiratory tract infection.[5] It may also be caused by a change to a higher altitude[3] and air travel. The partial pressure of inspired oxygen on commercial aeroplanes is only 110 to 130 mm Hg; this corresponds to a fraction of inspired oxygen of 0.15 to 0.17 at sea level.[6] Little is known about the physiological effects of airway hypoxia on respiratory function in infants. In adults acute airway hypoxia has pronounced effects on the control of breathing during sleep,[7] and respiratory control and oxygenation are considered to be more vulnerable to the effects of hypoxia and other insults during infancy. We became interested in the effects of airway hypoxia on respiratory control in infants after two sets of parents attending our outpatient clinic reported that their infants had died of the sudden infant death syndrome after intercontinental flights; one infant had died between 14 and 19 hours after a flight and the other had died between 40 and 41 hours later.

In this study we exposed clinically healthy infants to 15% oxygen in nitrogen to discover the effects of airway hypoxia on arterial oxygenation and on the frequency of isolated and periodic apnoeic pauses. We also wanted to determine if there was a subgroup of infants who would develop potentially significant hypoxaemia during exposure to 15% oxygen.

Subjects and methods

Subjects

Thirty four infants (20 boys) were enrolled in the study. Twenty one were recruited by structured sampling of births at an obstetric unit run by general practitioners and 13 by approaching families who were receiving support in caring for an infant after a previous infant had died of the sudden infant death syndrome. The two groups were matched for age at the time of the study (mean age 3.1 months, SD 1.7 months for the group recruited from the obstetric unit and 1.8 months for the group of infants whose siblings had died of the sudden infant death syndrome). To be enrolled, infants had to have been born at term and have no history of respiratory distress or congenital anomalies; later, one infant was found to have ß thalassaemia minor but it

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was considered inappropriate to exclude him retrospectively. Twelve mothers had smoked during their pregnancies, half of these were mothers of children whose deaths had been ascribed to the sudden infant death syndrome.

In the week before the study no infant had had an illness with fever, but four developed respiratory infections; two additional infants had coughs from previous infections. One infant died suddenly three weeks after the study at age 2 months. Her two older half-siblings had allegedly died of the sudden infant death syndrome. All three deaths were later identified as infanticide.

We had intended to study infants who had undergone apparent life threatening events. The first four infants enrolled after such events, however, had abnormally low baseline values of oxygen saturation in room air and thus could not be subjected to airway hypoxia. Apparent life threatening events in two other infants were found to be due to epilepsy[8] and intentional suffocation.[9] For these reasons we decided to concentrate on infants without a history of apparent life threatening events.

Informed consent

Parents were sent a standard letter which briefly discussed the methods and purpose of the study, including the potential relevance of the research to the mechanism that might be responsible for some deaths from the sudden infant death syndrome. A self addressed envelope and reply form were included. If families were interested in participating they were contacted and arrangements were made to discuss the project in more detail. This happened either at the family's home or by telephone, and when possible both parents were involved. Information was presented to parents on the relation between the administration of 15% oxygen and airline flights, holidays at altitude, and the sudden infant death syndrome.

All parents were aware that an overnight physiological recording of their infant's oxygen saturation and respiratory variables would be done at home before their child was exposed to hypoxic conditions in hospital. Parents were informed that this recording would be analysed to ensure that values were within normal limits before the infant was exposed to 15% oxygen. All parents knew that an experienced paediatrician would be present throughout the infant's exposure to 15% oxygen, and that exposure would end if the infant's oxygen saturation dropped to ≤80% for ≥1 minute. Where applicable parents were informed that this had been necessary during previous recordings in this study. Parents were aware that they could withdraw their baby from the study at any time without explanation. After this discussion parents were given another information leaflet and were asked to sign a consent form. Each of the families in which exposure to 15% oxygen was ended early because of hypoxaemia of ≤80% for ≥1 minute was advised against taking their infants on flights or to high altitude until they were older than 12 months. This study was approved by the local research ethics committees.

Measurement of respiratory variables

Three tape recordings were made over two nights for each infant. Signals recorded were oxygen saturation in beat-to-beat mode (N200 pulse oximeter, Nellcor, Hayward, CA), pulse waveforms for validation of the accuracy of saturation measurements, and abdominal breathing movements with a volume expansion capsule placed on the abdominal wall (Graseby Medical, Watford). Recordings were made at 60 to 120 m above sea level. Infants were placed in their normal sleep position (lateral or supine). The first recording (pre-challenge) was made in room air in the infant's home; the results were checked to verify that the infant had normal baseline oxygen saturation values (≥94%) before the second recording. The second and third recordings were made in hospital 1 to 4 days later (median 26 h). The second recording (challenge) took place in an oxygen tent[10] into which a medical gas mixture of 15% oxygen in nitrogen (British Oxygen Company, London) was delivered to maintain a monitored fraction of inspired oxygen of 0.15 to 0.16. Respired oxygen and carbon dioxide were monitored by a cannula on the upper lip (Elisa Duo, Engström, Stockholm) to confirm that rebreathing did not occur. Transcutaneous monitoring of the partial pressure of carbon dioxide was done at frequent intervals (Microgas, Kontron Instruments, Watford). Ambient temperature was maintained at 22°C to 26°C. Infants and monitors were observed continuously by an experienced paediatrician. According to our protocol, exposure to hypoxia would end if oxygen saturation fell to ≤80% for ≥1 minute. After the challenge infants were returned to room air and the third recording (post-challenge) was made throughout the rest of the night.

Recordings were printed and analysed manually by experienced technicians blind to the changes in inspired oxygen. Periods of regular and non-regular breathing patterns were identified[11]; a regular breathing pattern has been shown to be closely related to quiet sleep.[12] Apnoeic pauses lasting ≥4 s were identified; these were classified by duration (4 s to 7.9 s, 8 s to 11.9 s, and ≥12 s[13]) and by whether they were isolated or appeared in periodic apnoea (episodes of three or more pauses, each separated by <20 breaths[11]).

Baseline oxygen saturation, heart rate, and respiratory rate were measured only during episodes of a regular breathing pattern.[11] Periods when oxygen saturation fell to ≤80% for ≥4 s (desaturation) were identified throughout the recordings; these were classified as to whether they were associated with an apnoeic pause.[13] Mean values of transcutaneous partial pressure of carbon dioxide were calculated.

Results are presented as median and range, or mean and standard deviation. Statistical analysis was performed using the Wilcoxon matched pairs test for paired data and the Mann-Whitney U test for the group comparisons. Correlations were assessed by Spearman's rank test.

Results

There was no significant difference in any variable between infants who were recruited from the obstetric unit and those from families in which an infant had previously died of the sudden infant death syndrome. Only two variables, respiratory rate and heart rate, were correlated with age. Results from the pre-challenge, challenge, and post-challenge recordings are shown in the table.

Results of tests on infants done before, during, and after exposure to 15% oxygen. Values are medians (range)

				P values		
	Pre-challenge	Challenge	Post-challenge	Pre-challenge *v* challenge	Challenge *v* post-challenge	Pre-challenge *v* post-challenge
Measurements:						
Oxygen saturation (%)	97.6 (94.0 to 100)	92.8 (84.7 to 100)	97.5 (90.0 to 100)	<0.001	<0.01	>0.05
Heart rate/min	123 (105 to 140)	131 (107 to 146)	130 (99 to 144)	<0.01	>0.05	<0.05
Respiratory rate/min	30 (21 to 53)	32 (20 to 58)	31 (18 to 55)	>0.05	>0.05	>0.05
Percentage of time spent in regular breathing pattern	27 (0 to 53)	16 (0 to 44)	25 (7 to 83)	<0.001	<0.001	>0.05
No of episodes of desaturation/h	0 (0 to 0.2)	0.4 (0 to 35)	0 (0 to 0)	<0.001	<0.01	>0.05
Apnoea:						
Percentage of time spent in periodic apnoea	0.7 (0 to 31)	2.4 (0 to 35)	0.2 (0 to 11)	<0.001	<0.001	<0.05
Longest episode of periodic apnoea (min)	1.4 (0.9 to 20.5)	4.3 (0.4 to 34.8)	1.4 (0.5 to 4.8)	<0.01	<0.05	>0.05
Isolated apnoeic pauses/h	6.2 (0 to 13)	7.3 (0 to 19)	7.9 (0 to 17)	>0.05	>0.05	>0.05
Percentage of apnoeic pauses ⩾8 s	9.0 (0 to 33)	1.8 (0 to 47)	4.9 (0 to 50)	<0.001	<0.05	>0.05

The mean duration of the pre-challenge recordings was 7.7 (SD 2.1) hours. Data from these recordings were similar to data already reported.[13 14] Baseline oxygen saturation was ⩾94% in all infants, and only one infant had episodes of desaturation (three episodes, longest duration 11 s).

The mean duration of the recordings during the challenge was 6.3 (SD 2.9) hours. When compared with pre-challenge values, oxygen saturation during the challenge was lower (median difference −4.9%); this drop was highly variable (range −9.3% to 0.7%). Respiratory rates did not change significantly, but heart rates were 8 beats per minute higher ($P<0.01$); both rates were inversely correlated with age. Mean partial pressures of carbon dioxide during the challenge were within the normal range at 5.0 (SD 0.6) kPa. There was a significant decrease in the proportion of time spent in the regular breathing pattern, and a 3.5-fold increase overall in the proportion of time spent in periodic apnoea ($P<0.001$). There was a weak positive correlation between baseline oxygen saturation and amount of time spent in periodic apnoea ($r_s=0.44$, $P<0.01$) during challenge. The frequency of isolated apnoeic pauses did not change significantly. Pauses tended to be shorter than during pre-challenge recording, with a decrease from 9.0% to 1.8% in the proportion lasting ⩾8 s; none of the apnoeic pauses lasted ⩾20 s.

There was a significant increase in the number of times desaturation occurred per hour during hypoxia ($P<0.001$); 21 out of 34 (62%) recordings had episodes of desaturation. A median of 96% of episodes of desaturation (range 16% to 100%) were associated with apnoeic pauses and were short (median average duration 5.0 s, range 4.0 s to 7.2 s). The median of the average of the lowest oxygen saturation value occurring during desaturation was 72% (67% to 76%).

The mean duration of the post-challenge recordings was 4.5 (SD 1.9) hours. All variables returned to pre-challenge values except for heart rate (which remained significantly raised) and the proportion of time spent in periodic apnoea (which was significantly reduced). Exposure to hypoxia was ended early in six infants. Analysis of the recordings showed that for four of the six the decision to end exposure early was appropriate. Oxygen saturation had been ⩽80% for ⩾1 minute in three infants. Oxygen saturation had been ⩽80% for only 45 seconds in another infant but it had been <60% for two thirds of the time. Oxygen saturation values in the other two infants could not be interpreted because of movement artefact; a decision to withdraw these two infants from exposure to hypoxia was therefore inappropriate. However, while watching the monitoring the mother of one of these infants requested that her baby be returned to room air.

Withdrawal occurred after 1.9 to 5.2 hours (median 3.1 h) of hypoxic exposure in the four infants for whom it was appropriate; none of the infants woke spontaneously during their prolonged hypoxaemia. They were clinically well after withdrawal, although one received low flow oxygen (fraction of inspired oxygen 0.28) for the next hour to maintain oxygen saturation ⩾94%. None had recently had a respiratory illness; one was the sibling of an infant who had died of the sudden infant death syndrome. Their ages were similar to those of the complete sample. Three of the four, however, had had low baseline values of oxygen saturation during the challenge; they were three of the six infants in the complete sample who had values <90% during the challenge. The fourth did not have any periods of a regular breathing pattern during the challenge so baseline values could not be measured. None of the four infants who were withdrawn from exposure had prolonged apnoeic pauses on their recordings.

Discussion

Main findings and limitations of the study

These healthy 1 to 6 month old infants had highly variable and unpredictable responses to acute airway hypoxia; some infants became hypoxaemic to such a degree that their exposure to hypoxia was ended.

Some limitations of this study should be considered. We gave priority to describing the effects of several hours of acute airway hypoxia on sleeping infants, rather than to identifying the mechanisms of the observed responses. We tried to interfere as little as possible with the infants' normal sleep patterns and decided against recording electroencephalograms, electro-oculograms, or quantifying ventilation. This prevented us from collecting precise information about the reasons why some infants developed severe hypoxaemia when exposed to 15% oxygen. Possible explanations include hypoventilation[15] or increased inequalities between ventilation and perfusion.[16] We do not know why the infants who became severely hypoxaemic did not wake up. We do not know whether our experimental conditions are identical to those of air

Key messages

- A reduction in inspired oxygen concentration to 15% can induce severe prolonged hypoxaemia in a small proportion of infants
- Prediction of which infants will become hypoxaemic does not appear possible from analysing oxygenation or the respiratory pattern of infants breathing room air at sea level
- The way in which an infant responds to airway hypoxia may contribute to understanding the relation between respiratory infections, hypoxaemic episodes, and the sudden infant death syndrome
- Airline travel and holidays at high altitude may result in hypoxaemia in a small proportion of infants

travel and its effect on respiratory responses in infants. However, we could not find any data to suggest that there is a difference between a reduction in alveolar oxygen pressure due to reduced barometric pressure or due to a reduced fraction of inspired oxygen during constant atmospheric pressure. To address these issues infants would have to be studied during an airline flight or at high altitude.

Previous studies and possible relevance of these findings to the sudden infant death syndrome

Median values of baseline oxygen saturation during exposure to 15% oxygen in nitrogen in this study were similar to values measured by Lozano et al in 189 infants and young children born and living at 2640 m (93.3%, SD 2.1).[17] The range of values found in the study of Lozano et al was much narrower than the range found in our study. This difference in interindividual variability in baseline values may have occurred because the infants studied by Lozano et al might have been both genetically and environmentally adapted to airway hypoxia, whereas our infants were not. This idea is supported by the results of a study done in Lhasa (altitude 3660 m) which found that indigenous Tibetan infants had mean oxygen saturation values of 87% to 88% during sleep, while Chinese infants, who had recently moved to the region, had values of only 76% to 80%.[3] The lack of a genetic adaptation to high altitude has been proposed as the most likely cause for the disproportionately high rate of sudden deaths in infants soon after they have been moved to higher altitude.[3 4] High interindividual variability in the respiratory response to airway hypoxia may also explain why a proportion of infants with respiratory tract infections have low baseline values of oxygen saturation or an excessively high number of hypoxaemic episodes, or both.[5]

There was no difference in the response to airway hypoxia in infants with a sibling whose death had been ascribed to the sudden infant death syndrome or in infants without such a family history. This is in accordance with other studies which failed to find evidence for a disturbance in respiratory control or function in the siblings of infants who had died of the sudden infant death syndrome,[18 19] and reinforces doubts about the appropriateness of using such infants for investigations into the pathophysiology of the syndrome.

The most frequent cause of airway hypoxia in infants is respiratory infection (particularly bronchiolitis). We and others have shown that a small proportion of infants with such infections may progress to developing life threatening hypoxaemic episodes.[5 20] Respiratory infections have also been linked with the sudden infant death syndrome in a number of studies.[21]

Ethical issues

Was it ethically justified to expose healthy infants to 15% oxygen? Many infants travelling on aeroplanes or to holidays at high altitude are exposed to similar or even more markedly reduced partial pressures of inspired oxygen. Yet this exposure is considered safe. We were aware of anecdotal evidence of a small number of cases of the sudden infant death syndrome occurring after air travel, and of the observations made in Tibet.[4] We considered that information on this important issue should ideally have been gathered before infants were permitted to travel by air. We found no evidence that such studies had been done. Information collected by British Airways showed that one infant had died during a flight from Hong Kong to Britain (NJ Byrne, personal communication). Our protocol was designed to allow us to identify immediately any potentially harmful degree of hypoxaemia, hypoventilation, or effects on cardiac rhythm; infants were observed continuously by an experienced paediatrician who followed strict guidelines on when to end an infant's exposure to hypoxia. We must also emphasise that although the siblings of infants whose deaths had been ascribed to the sudden infant death syndrome were already being monitored at home, the majority of the infants in this study had not been seen in our clinic before the study. Their families were, therefore, unlikely to feel conscious or unconscious pressure to comply with our request for participation.

Clinical implications

We have shown that a small number of infants may become hypoxaemic during several hours of exposure to a fraction of inspired oxygen of 0.15 to 0.16. We could not, for ethical and humanitarian reasons, determine whether this would have progressed to clinically apparent cyanotic episodes if exposure had continued. Unfortunately, there was no physiological or clinical variable in this study which would help identify infants who might develop clinically important hypoxaemia during later exposure to airway hypoxia. We believe that additional research is urgently needed into the effects on infants of prolonged airline flights or holidays at high altitude. Our findings may contribute to an understanding of the possible relation between respiratory infection with resulting airway hypoxia and some sudden deaths in infancy.

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Contributors: DPS formulated the hypothesis and obtained funding for the study, he is also guarantor for the study. CFP, VAS, and DPS designed the protocol. DPS supervised the collection of clinical data which was largely collected by KJP and LMO. Parents were informed and supported by KJP. CFP, VAS, and LMO prepared the data and did the statistical analysis. CFP led the writing of the paper with the involvement of all authors. KJP produced the first draft of the paper.

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Commentary: Safety of participants in non-therapeutic research must be ensured

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When retrospectively evaluating research what matters is not the harm that actually resulted from the research, but the risk to which researchers exposed participants when all the knowledge available at the time is taken into account. At least five questions are relevant to this discussion.

Was there known to have been a risk to participants before the study began, and what was the magnitude of that risk as evaluated by the evidence available at the time?

There was evidence that a reduction in the pressure of inspired oxygen might be causally related to sudden infant death [1] at the time Parkins and colleagues began their study. Is it reasonable to impose a risk of death on healthy infants to gain more knowledge about physiological responses to hypoxia? It could be argued that monitoring procedures removed this risk. Even if the study design were perfect, the chance of human and mechanical error[2] could not be entirely removed.

This study is an example of non-voluntary, non-therapeutic research. It is generally accepted that the risk posed to participants by such research must be minimal.[3 4] The Royal College of Physicians suggests that participants in this type of research should be exposed to no more risk than that taken by a passenger flying on an aeroplane.[3] Indeed, the justification presented by the researchers for exposing normal infants to hypoxia is that "[m]any infants travelling on aeroplanes or to holidays at high altitude are exposed to similar or even more markedly reduced partial pressures of inspired oxygen. Yet this exposure is considered safe."

There are several problems with this argument. In the first place, researchers may have access to information which is not available to the public. Flying in an aeroplane may be more dangerous for some people—for example, those with emphysematous bullae. If an airline or responsible authority was unaware of the risks to travellers with emphysema they might allow them to travel on aeroplanes without restrictions. However, this would not provide justification for an interventional study which exposed these travellers to lower air pressures.

In the second place, even when information on risk is available some people behave recklessly; it would be opportunistic for researchers to take advantage of such behaviour. A prospective interventional study of behaviour during actual drink driving would be unethical even if resuscitation were available and there were no shortage of willing participants.

There is a related problem that occurs when judgments about the reasonableness of risk are based on assumptions drawn from behaviour. People judge that some risks are worth taking, but it is up to them to make that evaluation. Though driving a car or flying in an aeroplane does entail risk, it is wrong to assume that a person would take on this risk to participate in research. This is illustrated by the public's reaction to the scandal surrounding bovine spongiform encephalopathy. People may choose not to engage in an activity with a very small risk of death if they perceive that the benefits are outweighed by the risks. Were the parents in this study explicitly told that participation entailed a small risk to their infant's life? Participants must be scrupulously informed of such risks.

Standards of practice cannot be used to define the appropriate level of safety that should be provided to participants in research. We should look to the inherent risk. There are some concerns raised by this study by Parkins et al. Firstly, why was a saturation of ≤80% for

≥1 minute chosen as the criterion for ending exposure to hypoxia, and what evidence is there that it is safe to expose infants to hypoxia? Hypoxia was clearly clinically significant in some infants who were described as becoming "severely hypoxaemic." Indeed, one required supplemental oxygen for 1 hour.

Secondly, the methods section states: "Infants and monitors were observed continuously by an experienced paediatrician. According to our protocol, exposure to hypoxia would end if oxygen saturation fell to ≤80% for ≥1 minute." The results section states: "Oxygen saturation had been ≤80% for ≥1 minute in three infants." It is not clear from the protocol whether there was a definite upper limit to the time an infant might spend at an oxygen saturation below 80%. How long had oxygen saturation been ≤80% in these infants?

Thirdly, part of the reason for performing this study was because the researchers became aware of two infants who had died after travelling on an intercontinental flight. Why then did the follow up of infants exposed to hypoxia last only about 10 hours, given that one infant died 40 hours after travelling by aeroplane?

Should any non-human or epidemiological research, systematic overview, or computer modelling have been done before the study to better estimate the risk to participants or to eliminate the need to use human participants?

Piglets have been used as models for the physiological response of infants to hypoxia.[1]

Could the risk have been reduced in any other way?

Researchers could have asked parents of infants who were scheduled to travel on aircraft if their infants could participate. This increases the infants' risk by increasing their total exposure to hypoxia, but these infants and their parents would have the most interest in the results of the study. The results might have been relevant: parents of those infants who tolerated hypoxia poorly might have decided not to expose their infant to the risk of air travel.

Were the potential benefits of this study worth the risks? Was the study design adequate to increase understanding of responses to hypoxia in infants in aircraft and at high altitude?

The authors assert that there is nothing to suggest that a reduction in the fraction of inspired oxygen in reduced barometric pressure (as occurs in an aeroplane) does not have the same effect as a reduction in the fraction of inspired oxygen in constant atmospheric pressure (as in their experiment). Yet they admit that further study during an airline flight or at high altitude (or presumably in a hypobaric chamber) will be necessary. This raises a question about the design of their study: why wasn't the study done under the conditions described above instead of exposing some infants to risk in what must be described as a preliminary study?

Were the infants' parents made aware of all the relevant evidence, in particular evidence of the extent of the risk to the infants, and could the parents decide freely to participate or not based on the evidence of risk?

Concerns were expressed by the editorial committee before the paper was accepted for publication that because some parents already had a therapeutic relationship with the authors they might feel conscious or unconscious pressure to participate in the study. This is a difficult issue to evaluate because potential participants who are in a therapeutic relationship with the investigators may have the most to gain from a study and may have the strongest desire to participate for reasons of rational self interest or altruism. However, the Declaration of Helsinki requires that "informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship."[5]

I have raised concerns in this commentary over whether the risk to the infant was fully disclosed to parents. Doctors should now have serious concerns about infants being exposed to even mild hypoxia. The study by Parkins et al addresses an important issue and will no doubt add to the information available on the effects of hypoxia on infants. A balance must always be struck between discouraging relevant research which might eliminate continuing harm and making that research as safe and ethical as possible.

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Commentary: Ethical approval of study was warranted

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When the research ethics committee first reviewed the project proposed by Parkins and colleagues our immediate reaction was to reject the proposal because of fears about the possible danger to infants involved in the study. After our initial discussion, however, we recognised that the study might provide important information, not only on the sudden infant death syndrome but also on the safety of air travel for infants. It was also clear that the study could not be done on participants other than infants. We decided to invite Professor Southall to attend a committee meeting to respond to our concerns about doing non-therapeutic research on infants. The potential for risk had been made clear in the original submission; we hoped that Professor Southall would provide further information on the degree of risk that it was anticipated that infants would be exposed to.

Professor Southall attended the meeting on the 26 August 1992. After the meeting, committee members were convinced of the importance of the study, and reassured about the degree of monitoring and supervision that would occur during the infants' exposure to hypoxia. We were assured that exposure would end immediately if a baby became ill or experienced an unacceptably long period of apnoea or hypoxia and that appropriate treatment would be given if required. It was also established that parents would be informed of the nature and potential risks of the study in easily understood terms and that no coercion would be used to persuade parents to allow their infants to participate in the study.

The initial protocol indicated that only families in which an infant had died of the sudden infant death syndrome or in which an infant had had an apparent life threatening event would be asked to participate. We were later requested to permit the inclusion of a control group of healthy infants who had no known risk factors. This caused further heart searching debate, but we accepted that these healthy infants would be at less risk than those from families in which an infant had previously died of the sudden infant death syndrome or had had an apparent life threatening event; the control group was also exposed to less danger than a young child would be on a transatlantic flight. The committee was satisfied that all parents would be approached in a sympathetic manner and that requests for participation would include contacting the family's general practitioner.

Committee members were fully aware of the strict guidelines on the involvement of children in non-therapeutic research. We were also concerned about the potential for harm. However, after a final discussion, and after scrutinising the modified parent information and consent forms, we were convinced that the study should be allowed to proceed. We also feel that we would make the same decision today.

Authors' reply

K J Parkins, C F Poets, L M O'Brien, V A Stebbens, D P Southall

We considered that many healthy infants are exposed to airway hypoxia without apparent difficulties while travelling on airline flights or during holidays at high altitude when we assessed the risks that infants between the ages of 1 and 6 months would be exposed to in our study. It is not thought of as reckless to take infants on aeroplanes or on holidays at high altitude; no guidelines state that healthy infants should not be exposed to these activities.

Reviewing the literature in 1992 we found that non-indigenous infants born at altitude were at an increased risk of sudden death and mountain sickness.[1] We had also undertaken[2] and were aware of studies[3] linking airway hypoxia to apparent life threatening events. We also knew of two infants who had died of the sudden infant death syndrome shortly after an airline flight. We thought that by studying healthy infants in an environment of controlled hypoxia we might be able to elucidate issues relevant to the sudden infant death syndrome, apparent life threatening events, and the effects of respiratory infection. We did not believe that this information could be obtained through animal experiments (such as those mentioned in the commentary by Savulescu; these were published 3 years after our study began).

Research on children with cystic fibrosis has shown that hypoxia at sea level can accurately predict oxygen saturation during air travel.[4] Other studies have examined oxygen saturation at high altitude but mainly in indigenous populations which have a genetic adaptation to living in hypoxic conditions.[5] We considered performing our study in a hypobaric chamber but felt that this would cause difficulties in monitoring the infants, and might increase the risks to the infants because of difficulties in access.

Asking parents of infants who were scheduled to fly on aircraft to participate in the study might have created alarm or anxiety in parents before any results were known. Access to information about infants who are scheduled to fly is protected and difficult or impossible to obtain.

The facts about the study and its risks were presented clearly to the families. Parents were initially contacted by letter from a doctor who was not involved in their clinical care (KJP). They were invited to contact us for further information using a prepaid envelope. A more detailed discussion with a member of the research team then occurred and the parents were given written information. If they agreed to participate, consent was obtained. All parents were aware that there was a potential risk of their infant's blood oxygen saturation falling during exposure to 15% oxygen. They knew that their baby would be closely monitored by an experienced paediatrician and that if blood oxygen saturation fell below a threshold value the exposure would be ended. Before consenting to participate and when appropriate, families were informed that a proportion of infants studied earlier in the project had had episodes of desaturation when exposed to 15% oxygen. The families of those infants who had episodes of desaturation during our study were advised against taking the infant on an aeroplane or to high altitude until the infant was older; this is a potential benefit of being included in the study. All families knew that we had concerns about the safety of infants during airline travel; they knew that these concerns included a small risk of sudden death. Parents knew that they could withdraw their child from the study at any time without needing to justify their decision.

The degree of airway hypoxia that is safe for infants to be exposed to is unknown. We considered known baseline oxygen saturation levels at altitude[6] and normal ranges for episodes of desaturation in healthy infants[7] to guide us somewhat empirically in choosing a threshold value of oxygen saturation of $\leqslant 80\%$ for $\geqslant 1$

minute. Airway hypoxia was discontinued as soon as possible in each infant who showed this degree of desaturation; it should be remembered that this required the tent to be opened and the gas mixture to be removed from around the baby. No infant remained at ≤80% in 15% oxygen for longer than 126 seconds.

Of the four infants in whom exposure to hypoxia was discontinued early, one infant had a sibling who had died of the sudden infant death syndrome and was already being monitored at home. Oxygen saturation levels in all four infants remained within the normal range during subsequent monitoring. We believed that monitoring the infants for a longer period in hospital would not have been ethically appropriate because they might be exposed to additional risks (for example, the risk of acquiring an infection in hospital). The two infants who had died following an aircraft flight were not monitored so we are unaware of the duration and degree of hypoxaemia to which they might have been exposed.

Although Savulescu's commentary raises the spectre of human or mechanical error, we took every precaution to ensure that the infants were safe. These included the use of a special medical gas mixture of 15% oxygen and 85% nitrogen instead of air diluted with nitrogen, continuous monitoring of the partial pressure of inspired carbon dioxide to identify rebreathing, and continuous monitoring of the partial pressure of inspired oxygen to ensure adequate ventilation of the tent with the gas mixture. The study was done in a room near the intensive care unit. There was also continuous surveillance by an experienced paediatrician of the readings from the pulse oximeter, transcutaneous monitoring of the partial pressure of carbon dioxide, monitoring of respiratory movement, and electrocardiography.

Although Milner reports in his editorial that British Airways identified no deaths on the undisclosed number of flights involving infants, this is low quality information. It is not accurate, as shown by the personal communication cited in our paper. Infant stimulation and the attention paid to an infant during an airline flight may delay potentially serious consequences of the flight until after the plane's arrival. British Airways would not have access to information on infants after arrival and did not seem to know about either of the two cases of the sudden infant death syndrome that were described in our report.

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Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials

Homocysteine Lowering Trialists' Collaboration

Participants in the collaboration are listed at the end of the paper

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Abstract

Objective: To determine the size of reduction in homocysteine concentrations produced by dietary supplementation with folic acid and with vitamins B-12 or B-6.

Design: Meta-analysis of randomised controlled trials that assessed the effects of folic acid based supplements on blood homocysteine concentrations. Multivariate regression analysis was used to determine the effects on homocysteine concentrations of different doses of folic acid and of the addition of vitamin B-12 or B-6.

Subjects: Individual data on 1114 people included in 12 trials.

Findings: The proportional and absolute reductions in blood homocysteine produced by folic acid supplements were greater at higher pretreatment blood homocysteine concentrations ($P<0.001$) and at lower pretreatment blood folate concentrations ($P<0.001$). After standardisation to pretreatment blood concentrations of homocysteine of 12 μmol/l and of folate of 12 nmol/l (approximate average concentrations for Western populations), dietary folic acid reduced blood homocysteine concentrations by 25% (95% confidence interval 23% to 28%; $P<0.001$), with similar effects in the range of 0.5-5 mg folic acid daily. Vitamin B-12 (mean 0.5 mg daily) produced an additional 7% (3% to 10%) reduction in blood homocysteine. Vitamin B-6 (mean 16.5 mg daily) did not have a significant additional effect.

Conclusions: Typically in Western populations, daily supplementation with both 0.5-5 mg folic acid and about 0.5 mg vitamin B-12 would be expected to reduce blood homocysteine concentrations by about a quarter to a third (for example, from about 12 μmol/l to 8-9 μmol/l). Large scale randomised trials of such regimens in high risk populations are now needed to determine whether lowering blood homocysteine concentrations reduces the risk of vascular disease.

Introduction

Epidemiological studies have consistently reported that patients with occlusive vascular disease have higher blood homocysteine concentrations than control subjects, and that these differences precede the onset of disease and are independent of other risk factors.[1–5] A meta-analysis of the observational studies of blood homocysteine and vascular disease indicated that a prolonged lowering of homocysteine concentration by 1 μmol/l was associated with about a 10% reduction in risk throughout the range 10-15 μmol/l.[1] Blood concentrations of homocysteine are inversely related to blood concentrations of folate, vitamin B-12, and, to a lesser extent, vitamin B-6.[6] Dietary supplements of these vitamins are used to reduce homocysteine concentrations in subjects with homozygous homocystinuria, who have particularly high blood concentrations of homocysteine.[7] Several randomised controlled trials of the effects of folic acid based supplements on homocysteine concentrations have been conducted. Our study aimed, by a meta-analysis of data from individual participants in these trials, to determine more reliably the size of the reduction in blood homocysteine achieved with different doses of folic acid and with the addition of vitamin B-12 and vitamin B-6. This should help in the design of randomised trials of the effects of lowering homocysteine concentrations on vascular disease.

Methods

Studies included

We aimed to identify all published and unpublished randomised trials that had assessed the effects on blood homocysteine concentrations of folic acid supplements, with or without the addition of vitamins B-12 or B-6. Studies were not eligible if they did not include an untreated control group, assessed treatment after methionine loading, or treated patients for less than 3 weeks.[8–15] Eligible studies were identified by Medline searches (using search terms and widely used variants for folic acid, vitamin B-12, vitamin B-6, and homocysteine, and including the non-English language literature), scanning reference lists, and personal contact with relevant investigators. The 14 trials we identified that fulfilled the eligibility criteria[16–24] included two completed trials (involving 50 and 144 subjects; V Howard, I Brouwer, personal communications) from which data are not available for collaborative analyses until their publication. The 12 available trials included 1114 subjects. Ten of these trials had a parallel group design[16–24] and two had a crossover design[21] (for which, to avoid any carryover effects, we used only data from the first period). The allocated treatment was blinded in all trials except two that had untreated controls.[16 23]

Information collected

For each subject entered in these trials, we sought details of age, sex, smoking habits, history of vascular disease or hypertension, and vitamin use before randomisation, and of their randomly allocated treatment regimen (daily dose of folic acid, vitamin B-12 or vitamin B-6, and scheduled duration) and blood concentrations of homocysteine, folate, vitamin B-12, and vitamin B-6 before treatment and at the end of the scheduled treatment period.

Table 1 Characteristics of the 12 available trials of treatment based on folic acid

Report	No of patients	Mean age (years)	Treatment duration (weeks)	Median pretreatment concentration: Homocysteine (μmol/l)	Median pretreatment concentration: Folate (nmol/l)
Brattström[16]	53	65	6	14.3	13.0
Den Heijer I[17]	52	56	8	17.2	9.7
Den Heijer II[17]	178	53	8	11.9	12.7
Den Heijer III[17]	92	61	8	13.6	12.1
Ubbink I[18]	91	39	6	24.9	4.7
Ubbink II[19]	26	40	6	20.6	4.7
Naurath[20]	285	75	3	12.4	9.7
Pietrzik I[21]	70	25	12	7.4	23.1
Pietrzik II[21]	128	25	4	7.5	21.3
Woodside[22]	112	40	8	9.8	9.2
Cuskelly[23]	17	23	12	5.6	6.4
Saltzman[24]	10	58	4	14.4	19.9
Total	1114	52	6	11.8	11.6

Statistical analysis

The proportional reductions in blood homocysteine in the treated groups compared with the control groups were determined by extending an analysis of covariance[25] that estimated the differences in post-treatment, log transformed homocysteine values after adjustment for baseline values of homocysteine. The simple model was extended to allow the extent of this adjustment to vary between studies and to take account of factors such as folic acid dose, concomitant vitamin B-12 or vitamin B-6, age, sex, and duration of treatment. More complex models that allowed the effect of folic acid supplementation to differ in individual studies were used to investigate sources of heterogeneity.

Results

Characteristics of individual trials

Among the 1114 subjects in the trials, the mean age was 52 years (range of trial means 23 to 75 years) and the mean duration of treatment was 6 weeks (range 3 to 12 weeks) (table 1). The median pretreatment blood concentration of homocysteine was 11.8 μmol/l and of folate was 11.6 nmol/l, but there were substantial differences between the trials. All of the trials compared folic acid alone versus control or folic acid plus vitamin B-6 or B-12, or both, versus control, although two trials[17 18] also involved within-trial comparisons of folic acid alone versus combination therapy (table 2). A correlation coefficient of 0.87 for homocysteine in pretreatment blood samples collected from 664 of these patients on two separate occasions shows that there was relatively little variation within subjects and that the homocysteine measurements were reliable. Compliance with the study protocols was good, with blood homocysteine measurements at the end of study treatment available from 98% of those randomised.

Exploration of heterogeneity between the results of different trials

The effect of folic acid on blood homocysteine concentrations seemed to differ among the trials. This heterogeneity of the homocysteine lowering effect was not explained by differences in age, sex, or duration of treatment (although the longest duration studied was only 12 weeks). The proportional and absolute reductions in blood homocysteine concentrations seemed, however, to be influenced by the pretreatment blood concentrations of homocysteine and folate, but not of vitamin B-12. Even after adjustment for differences in the folic acid regimen, the homocysteine lowering effect of folic acid ranged from a proportional reduction of 16% (11% to 20%) among subjects in the bottom fifth of pretreatment blood homocysteine concentrations to a 39% (36% to 43%) reduction among those in the top fifth (fig 1; P for trend <0.001). Conversely, the blood homocysteine lowering effect of folic acid was greater at lower pretreatment blood concentrations of folate (P for trend <0.001). These associations of the homocysteine lowering effect with pretreatment concentrations of blood homocysteine and blood folate remained significant ($P<0.001$) when both pretreatment measurements were included simultaneously in the model. The model provided no strong evidence that the variation in the homocysteine lowering effect with baseline homocysteine depended on baseline folate or vice versa. Figure 2 shows that the proportional reductions in blood homocysteine concentrations achieved by folic acid supplementation according to pretreatment blood levels of homocysteine and folate under this assumption. (Exclusion of the two trials[18 19] in subjects with very high pretreatment blood homocysteine concentrations did not materially alter these findings, and nor did inclusion of the two small completed but unpublished trials not yet formally available for these collaborative analyses: data not shown.)

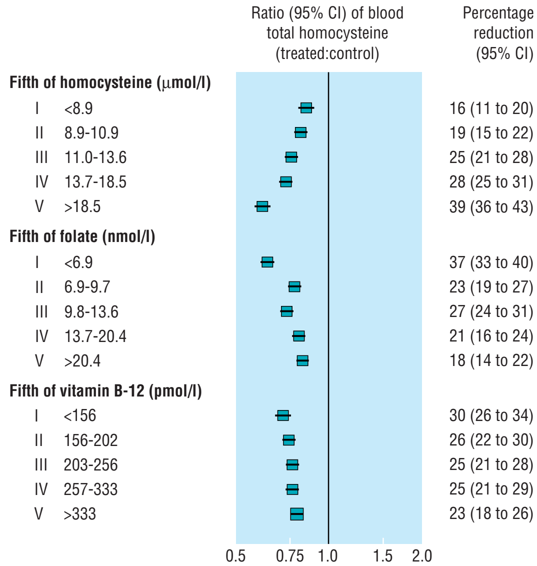

Fig 1 Reductions in blood homocysteine concentrations with folic acid supplements according to pretreatment blood concentrations of homocysteine, folate, and vitamin B-12. Squares indicate the ratios of post-treatment blood homocysteine among subjects allocated folic acid supplements to those of controls; size of square is proportional to number of subjects, and horizontal line indicates 95% confidence interval

Table 2 Blood concentrations of homocysteine in individual trials

Report	Treatment comparisons with doses of vitamins	No of patients	Mean homocysteine concentration (μmol/l)			
			Pretreatment	Post-treatment	Difference (SD)	Ratio (SD)
Brattström[16]	Untreated control	20	14.5	15.1	0.6 (1.2)	1.0 (0.1)
	2.5 mg folate	16	16.9	12.0	–4.9 (3.9)	0.7 (0.2)
	10 mg folate	17	15.8	11.3	–4.5 (3.5)	0.7 (0.1)
Den Heijer I[17]	Placebo	27	18.9	17.8	–1.1 (5.6)	1.0 (0.2)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	25	18.7	11.3	–7.0 (7.0)	0.7 (0.2)
Den Heijer II[17]	Placebo	36	11.9	11.4	–0.6 (2.7)	1.0 (0.2)
	0.5 mg folate	36	12.4	9.7	–2.8 (2.4)	0.8 (0.2)
	5 mg folate	35	12.1	8.9	–3.2 (2.2)	0.8 (0.1)
	0.4 mg B-12	36	12.6	11.3	–1.3 (2.0)	0.9 (0.2)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	35	12.1	8.3	–3.8 (3.9)	0.7 (0.2)
Den Heijer III[17]	Placebo	46	14.0	14.5	0.5 (5.6)	1.0 (0.4)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	46	15.9	10.3	–5.7 (9.7)	0.7 (0.2)
Ubbink I[18]	Placebo	17	30.0	30.7	–0.7 (9.1)	1.0 (0.3)
	0.6 mg folate	19	28.4	16.8	–11.6 (6.2)	0.6 (0.2)
	10 mg B-6	17	28.2	27.9	–0.3 (9.6)	1.0 (0.4)
	0.4 mg B-12	18	30.6	26.0	–4.6 (9.1)	0.9 (0.3)
	0.6 mg folate, 0.4 mg B-12, 10 mg B-6	20	26.9	13.6	–13.3 (7.3)	0.5 (0.2)
Ubbink II[19]	Placebo	13	23.5	22.1	–1.4 (4.8)	1.0 (0.2)
	1 mg folate, 0.4 mg B-12, 10 mg B-6	13	29.3	11.5	–17.8 (13.8)	0.5 (0.2)
Naurath[20]	Placebo	142	13.9	13.4	–0.5 (2.7)	1.0 (0.2)
	1.1 mg folate, 1 mg B-12, 5 mg B-6	143	12.7	8.4	–4.4 (3.5)	0.7 (0.2)
Pietrzik I[21]	Placebo	37	8.1	8.7	0.6 (1.2)	1.1 (0.1)
	0.4 mg folate, 0.1 mg B-12, 2 mg B-6	33	7.2	5.8	–1.4 (1.3)	0.8 (0.2)
Pietrzik II[21]	Placebo	86	8.1	8.2	0.2 (1.4)	1.0 (0.2)
	0.4 mg folate, 2 mg B-6	42	7.8	6.6	–1.2 (1.2)	0.9 (0.1)
Woodside[22]	Placebo	55	9.9	9.0	–0.9 (1.8)	0.9 (0.2)
	1 mg folate, 0.02 mg B-12, 7.2 mg B-6	57	11.9	7.8	–4.3 (3.4)	0.7 (0.1)
Cuskelly[23]	Untreated control	8	7.0	6.7	–0.2 (0.7)	1.1 (0.1)
	0.4 mg folate	9	5.8	5.0	–0.8 (1.0)	0.9 (0.2)
Saltzman[24]	Placebo	5	11.5	12.2	0.7 (1.5)	1.1 (0.1)
	2 mg folate	5	19.6	15.0	–4.6 (3.5)	0.8 (0.1)

Effects of different folic acid doses on blood homocysteine

After pretreatment blood concentrations of homocysteine and folate were adjusted for, there was no longer much evidence of heterogeneity between the separate blood homocysteine lowering effects in the different trials of daily folic acid doses of <1 mg (mean dose 0.5 mg; P value for heterogeneity=0.15), of 1-3 mg (mean dose 1.2 mg; P=0.05), or of >3 mg folic acid (mean dose 5.7 mg; P=0.69). Nor was there any evidence of differences between the blood homocysteine lowering effects of these different folic acid doses. For individuals with pretreatment blood concentrations of homocysteine of 12 µmol/l and of folate of 12 nmol/l (approximate average concentrations for Western populations), folic acid doses of <1 mg, 1-3 mg, and >3 mg daily were each associated with reductions in blood homocysteine of about one quarter (fig 3).

Homocysteine concentrations before randomisation (µmol/l)	Folate concentrations before randomisation (nmol/l): 20	15	12	10	5
5	10%	13%	15%	16%	23%
10	19%	21%	23%	25%	30%
12	21%	23%	25%	27%	32%
15	23%	26%	28%	29%	34%
20	27%	29%	31%	32%	37%

Fig 2 Predicted proportional reduction in blood homocysteine concentrations with folic acid supplementation (0.5-5 mg daily)

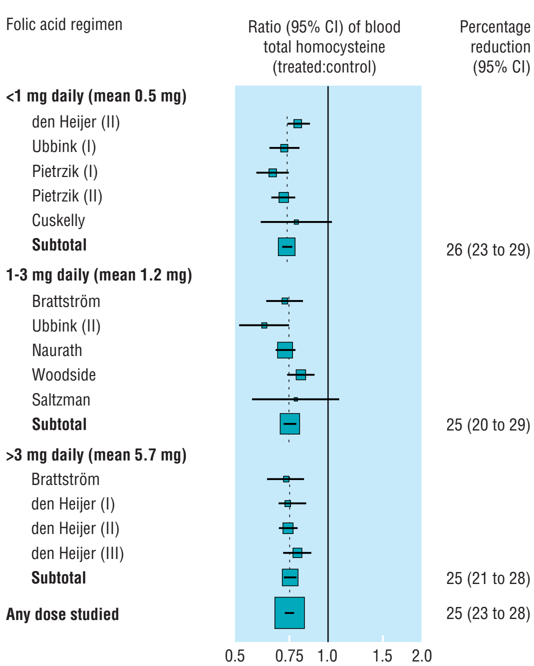

Fig 3 Reductions in blood homocysteine concentrations with varying doses of folic acid at pretreatment blood concentrations of homocysteine of 12 µmol/l and folate of 12 nmol/l. Squares indicate the ratios of post-treatment blood homocysteine among subjects allocated folic acid supplements to those of controls; size of square is proportional to number of subjects, and horizontal line indicates 95% confidence interval

Effects of adding vitamin B-12 or vitamin B-6 to folic acid

The addition of vitamin B-12 (0.02-1 mg daily; mean 0.5 mg) to folic acid further reduced blood homocysteine concentrations by about 7% (3% to 10%). Hence, among people with pretreatment blood concentrations of homocysteine of 12 µmol/l and of folate of 12 nmol/l, adding vitamin B-12 to folic acid changed the reduction in homocysteine from 25% (23% to 28%) to 31% (27% to 35%). Adding vitamin B-6 (2-50 mg daily; mean 16.5 mg) to folic acid did not lower blood homocysteine any further.

Discussion

Among the vitamins studied in these trials, folic acid had the dominant blood homocysteine lowering effect, and this effect was greater among subjects with higher blood homocysteine concentrations or lower blood folate concentrations before treatment. After standardisation for differences in pretreatment blood homocysteine and folate concentrations, the effect of folic acid was similar for daily doses ranging from 0.5 to 5 mg daily, and vitamin B-12 produced a small additional effect. Supplementation with vitamin B-6 did not seem to have any material effect on blood homocysteine concentrations, but these trials did not assess effects on blood homocysteine after methionine loading, which may be determined to a greater extent by the transulphuration pathway in which vitamin B-6 is a cofactor.[8]

Our results suggest that a daily dose of at least 0.5 mg of folic acid, along with a similar amount of vitamin B-12, would produce a proportional reduction in blood homocysteine of about a quarter to a third. The addition of about 1 mg daily of oral vitamin B-12 to folic acid would also be expected to avoid the theoretical risk of neuropathy due to unopposed folic acid therapy in patients deficient in vitamin B-12, even those with intrinsic factor deficiency or malabsorption states.[26-28] Studies in the United States and Britain indicate that the average concentration of blood homocysteine in a typical Western population is about 12 µmol/l,[4 6] and so a reduction of about a quarter to a third would correspond to an absolute reduction of about 3-4 µmol/l. A previous meta-analysis of the observational studies suggests that a prolonged lower blood homocysteine concentration of 3-4 µmol/l would correspond to 30-40% less vascular disease.[1] Consequently, even if as much as half of the epidemiologically predicted benefit is achieved within a few years of lowering blood homocysteine (as seems to be the case with cholesterol lowering[29-31]), trials of folic acid supplements may well need to be large, and to include people at high risk, to be able to detect the sort of reductions—15% to 20%—in cardiovascular risk that might realistically be anticipated.

Supplementation with folic acid is a cheap and effective method of lowering blood homocysteine concentrations. If large scale trials in high risk populations do show reliably that blood homocysteine reductions with such supplements can be sustained over time and that this strategy reduces the risk of vascular events (and is safe), this could have important public health implications. Higher dose supplements could be used in people at high risk, and population mean

Key messages

- Higher blood homocysteine concentrations seem to be associated with higher risks of occlusive vascular disease and with lower blood concentrations of folate and vitamins B-12 and B-6
- Proportional and absolute reductions in blood homocysteine concentrations with folic acid supplements are greater at higher pretreatment blood homocysteine concentrations and at lower pretreatment blood folate concentrations
- In typical Western populations, supplementation with both 0.5-5 mg daily folic acid and about 0.5 mg daily vitamin B-12 should reduce blood homocysteine concentrations by about a quarter to a third
- Large scale randomised trials of such regimens in people at high risk are now needed to determine whether lowering blood homocysteine concentrations reduces the risk of vascular disease

concentrations of blood homocysteine could be reduced by fortifying flour with folic acid.[1 32] Introducing fortified flour for the prevention of neural tube defects before trials of folic acid on vascular disease are conducted could, however, complicate the overall assessment of any benefits—or risks—of lowering homocysteine concentrations in this way.

The following investigators were members of the Homocysteine Lowering Trialists' Collaboration. Abbreviated trial names are listed alphabetically, along with the institutions and names of the principal investigators. Brattström (University of Lund: L Brattström, F Landgren, B Israelsson, A Lindgren, B Hultberg, A Andersson); Cuskelly (University of Ulster: G Cuskelly, H McNulty, SS Strain; Trinity College, Dublin: J McPartlin, DG Weir, JM Scott); den Heijer (Leyenburg Hospital, the Hague, and University of Nijmegen: M den Heijer, IA Brouwer, HJ Blom, GMJ Bos, A Spaans, FR Rosendaal, CMG Thomas, HL Haak, PW Wijermans, WBJ Gerrits); Naurath (University of Leuven and Witten-Herdecke: HJ Naurath, E Joosten, R Riezler, SP Stabler, RH Allen, J Lindenbaum); Pietrzik (University of Bonn: K Pietrzik, R Prinz-Langenohl, J Dierkes); Saltzman (USDA-HNRC at Tufts University: E Saltzman, JB Mason, P Jacques, J Selhub, D Salem, E Schaefer, IH Rosenberg); Ubbink (University of Pretoria: J Ubbink, A van der Mere, WJH Vermack, R Delport, PJ Becker, HC Potgieter); Woodside (Queen's University of Belfast: JV Woodside, JWG Yarnell, D McMaster, IS Young, EE McCrum, SS Patterson, KF Gey, AE Evans).

Secretariat: Clinical Trial Service Unit, University of Oxford (R Clarke, P Appleby, P Harding, P Sherliker, R Collins) and Medical Statistics Unit, London School of Hygiene and Tropical Medicine (C Frost, V Leroy).

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Mental health problems of homeless children and families: longitudinal study

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Abstract

Objective: To establish the mental health needs of homeless children and families before and after rehousing.
Design: Cross sectional, longitudinal study.
Setting: City of Birmingham.
Subjects: 58 rehoused families with 103 children aged 2-16 years and 21 comparison families of low socioeconomic status in stable housing, with 54 children.
Main outcome measures: Children's mental health problems and level of communication; mothers' mental health problems and social support one year after rehousing.
Results: Mental health problems remained significantly higher in rehoused mothers and their children than in the comparison group (mothers 26% *v* 5%, P = 0.04; children 39% *v* 11%, P = 0.0003). Homeless mothers continued to have significantly less social support at follow up. Mothers with a history of abuse and poor social integration were more likely to have children with persistent mental health problems.
Conclusions: Homeless families have a high level of complex needs that cannot be met by conventional health services and arrangements. Local strategies for rapid rehousing into permanent accommodation, effective social support and health care for parents and children, and protection from violence and intimidation should be developed and implemented.

Introduction

Following research on the health problems of single adult homeless people, there has been interest in the characteristics and needs of homeless children and their families, who constitute a different and rapidly growing population.[1] At any one time, at least 60 000 families, with between 140 000 and 170 000 children, are defined as homeless by local authorities in England.[2 3] In addition, the number of single homeless teenagers living on the streets is increasing, as is the number of homeless families living with friends and relatives or in squats.

The causes of homelessness in this group are diverse: many are victims of domestic violence,[4] and the group also includes refugee families, mainly in the London area.[5] Homeless children are significantly more likely than the general population, or comparison children in stable housing, to have delayed development,[6] learning difficulties,[7] and higher rates of mental health problems (behavioural problems such as sleep disturbance, eating problems, aggression, and overactivity, and emotional problems such as depression, anxiety, and self harm).[6 8–10] Such problems are not specific to homeless families. They occur in other families living in adversity and have been found to be related to adverse life events that precipitate homelessness—for example, family breakdown, abuse, exposure to domestic violence, and poor social networks.[10]

Because many homeless families have changed address frequently or urgently, they are less likely than the rest of the population to be registered with a general practitioner.This reduces their access to primary and secondary medical care, as well as to immunisations and other preventive health procedures. Homeless families therefore tend to rely on accident and emergency departments for medical treatment, and they have high rates of hospital admission.[11] To date, there has been no research on the long term impact of homelessness on the mental health of children and their families. This cross sectional longitudinal study was designed to establish the extent of mental health problems among homeless children and their parents one year after rehousing by the local authority.

Subjects and methods

Subjects

Subjects were selected from a sample described in an earlier cross sectional study on homeless families.[10] This included 113 homeless families who had applied for rehousing to the City of Birmingham's housing department and who had been admitted to the seven homeless centres managed by the department over one year. These were initially interviewed within two weeks of becoming homeless and being admitted to the hostel. A comparison group of 29 housed, low income families had been selected from two schools where homeless children attended at the time, by random selection from the school list. All families were of socioeconomic class V.[12] A relatively small comparison sample was selected because of the expected "homogeneity" (low variance of family and social variables) in a stable community population. Parents were asked to give informed consent, after approval by two local research ethics committees.

Our study was conducted one year after the initial assessment of both groups. Homeless families had already given consent to be contacted at follow up, and their new address was sought from the housing department. Although only seven families (6%) refused to be interviewed again at this stage, a substantial proportion (40 families, 35%) had already moved from their follow up address and were untraceable, and 8 (7%) had left the centre before being rehoused by the local authority. At one year, we interviewed 58 families (51% of initial sample) with 103 children aged 2-16 years who were in housing and constituted the study group, and 21 comparison families (72% of initial sample) with 56 children aged 2-16 years. Families lost to follow up did not differ from those interviewed at one year in regard to family composition, demographic factors, or reasons for becoming homeless. Children younger than 2 years were not included because there is no reliable way of establishing behavioural and emotional problems for such a young age group. Because of the small number of fathers involved at intake[10] and follow up (table 1), data analysis was confined to mothers. All comparison families interviewed at follow up had remained in the same residence over the 12 month period.

Assessment

Five research instruments were used to assess mental health problems.

Semi-structured interview with the mother—this consisted of questions concerning house moves, family life, peer and family relationships, and behavioural problems among the children. Mothers were interviewed at the hostel by a research psychologist (EG).

Child behaviour checklist—this questionnaire has been widely used in research to measure externalising (behavioural) and internalising (emotional) problems, and social competence (activities, peer relationships, and school performance) in children.[13] It has been standardised in large community and clinical populations. Adapted scores (T scores) indicate whether the child is within the "clinical range" (problem of sufficient severity to be referred for treatment to a child mental health service: T score $\geqslant$63) or within the "social maladjustment" range (T score $\leqslant$37). A parent completed a separate questionnaire for each child in the survey. In the case of children aged 2-3 years, the version used excluded social competence questions.[14]

General health questionnaire—this is an established and standardised screening questionnaire for use in surveys of adult mental health problems in the general population.[15] A 28-item version was used in this study, which generates scores for somatic symptoms, anxiety, social dysfunction, and depression. Cut off scores have been established to identify possible mental health disorders (caseness). A questionnaire was completed by each mother.

Interview schedule for social interaction—this is a measure of people's social network.[16 17] It includes scales that measure the availability and perceived adequacy of attachment relationships, the availability and perceived adequacy of social integration, and the number of attachment relationships with whom the respondent has recently been having rows or unpleasant interaction with.[17]

Table 1 Characteristics of homeless families (one year after rehousing) and of low income families in stable housing

Characteristic	Rehoused (n=58)	Comparison (n=21)	Difference
No (%) single mothers	40 (69)	7 (33)	χ^2=21.2, P<0.001
No (%) two parent families	18 (31)	14 (66)	
Median (range) No of children	2 (1-5)	3 (1-7)	*t*=1.1, NS
Mean (range) age of mother (years)	31 (20-44)	32.4 (26-46)	*t*=1.1, NS
Mean (range) age of children (years)	8.5 (3-16)	9.4 (3-16)	*t*=1.7, NS
No (%) boys	54 (52)	28 (52)	χ^2=0.005, NS
Mother's ethnic group:			
White	48 (83)	14 (67)	χ^2=7.7, P=0.02
Afro-Caribbean	6 (10)	2 (10)	
Asian	4 (7)	5 (24)	
Mother's occupation:			
Unemployed	47 (81)	14 (67)	χ^2=6.5, NS
Full time work	1 (2)	2 (10)	
Part time work	7 (12)	5 (24)	
Full time education	3 (5)	0	

Communication domain of the Vineland adaptive behaviour scales—this measures the development of communication in children.[18] Scores are adapted according to norms from the general population; an age equivalent score is provided and indicates the chronological age at which the child is functioning.

Statistical analysis

Within the homeless group, mental health scores at the first and follow up assessment were compared by Wilcoxon matched pairs, signed ranks test. Between-group analyses (homeless and comparison families) were done with χ^2 test, *t* test, and Mann-Whitney non-parametric U test, depending on the nature and distribution of the data.

Results

Family characteristics and housing

Family characteristics are presented in table 1. Because hostels for homeless Asian and Afro-Caribbean families were run by the voluntary sector and were not included in the initial study, ethnic minority groups were underrepresented in the rehoused group in comparison with both the housed group ($\chi^2 = 7.7$, df = 2, P = 0.02) and the local general population (inner Birmingham wards have up to 12.5% Afro-Caribbean and 43% Asian children). At the time of the first assessment,[10] the most common reason for becoming homeless was to escape from violence, either by a partner or ex-partner (29, 50%) or by neighbours (20, 35%). Other families had become homeless after eviction from their previous housing because of mortgage or rent arrears (3, 5%); 6 (11%) had left voluntarily or for other reasons.

The average length of stay in the homeless centre for the families who were reinterviewed was 10 weeks (range 2-58 weeks). The housing department's target is to rehouse within 28 days. Thirty five families (60%) moved to the first property offered. At follow up, 17 families (30%) had moved at least once in the year and 9 (16%) had been homeless again at some time. Of those who had moved since being rehoused, 29 (50%) gave violence or harassment from an ex-partner or neighbours as the reason for their move. Seventeen families (30%) were unhappy with the property they had been allocated, and 20 (35%) were not happy with the area. At follow up, 52 families (90%) lived in rented property, two (3%) in owned property, three (5%) in a homeless centre, and one family (2%) was lodging with friends. Eighteen comparison families (81%) lived in rented property and four (22%) in owned property (χ^2 for difference = 6.5, df = 3, P = 0.09).

Mental health problems

Mothers

Homeless mothers had high rates of previous abuse (25 (43%) *v* 1 (5%) control mother, $\chi^2 = 10.6$, P = 0.001). On the basis of general health questionnaire scores, the rate of homeless mothers who reported mental health problems of clinical significance had decreased from 52% at initial interview to 26% at one year follow up, and total scores significantly decreased for the homeless group (P = 0.002, Wilcoxon test). However, at follow up the scores remained significantly higher than those of comparison mothers (table 2) or the general population (up to 20% for women of this age group).[19]

Children

Seven children had been in care before becoming homeless and two since rehousing. Twelve children had been placed on the at risk child protection register before they became homeless, and six since being rehoused; 10 children had a history of physical or sexual abuse. No comparison children were reported to have had similar adversities.

Though homeless children improved on the Vineland communication scores, this did not reach statistical significance (P = 0.07, Wilcoxon test), and they remained significantly more delayed than children in the comparison group (table 2). Homeless children's age equivalent of communication remained significantly lower than their chronological age (age equivalent 7.8 years *v* chronological age 8.5 years; P = 0.0001), unlike controls (age equivalent 9.1 years *v* chronological age 9.4 years; P = 0.16). Homeless children's scores on the child behaviour checklist showed no significant change (58.2 at baseline *v* 59.2 at follow up; P = 0.53), and they remained significantly more likely to be within the clinical range than the comparison group.

Table 2 Mental health problems in mothers and children at one year follow up. Values are numbers (percentages) unless specified otherwise

	Rehoused group	Comparison group	Difference*
Mothers	(n=58)	(n=21)	
General health questionnaire:			
Caseness†	15 (26)	1 (5)	χ^2=4.3, P=0.04
Mean (SD) total score	29.9 (16.5)	18.1 (9.6)	z=2.9, P=0.004
Interview schedule for social interaction:			
Availability of attachment relationships	4.7 (2.2)	7.1 (1.1)	z=4.3, P<0.0001
Perceived adequacy of attachment relationships	7.1 (3.7)	10.6 (1.1)	z=3.6, P=0.0003
Availability of social integration	7.0 (3.2)	10.7 (4.6)	z=3.3, P=0.0008
Perceived adequacy of social integration	10.4 (4.8)	13.9 (2.1)	z=2.8, P=0.005
Children	(n=103)	(n=54)	
Child behaviour checklist:			
Caseness	40 (39)	6 (11)	χ^2=12.9,P=0.0003
Social maladjustment‡	71 (69)	33 (61)	χ^2=3.7, P=0.05
Mean (SD) score	59.2 (8.7)	49.2 (9.1)	z=5.8, P<0.0001
Mean (SD) internalising	55.1 (12.1)	49.4 (9.3)	z=2.8, P=0.005
Mean (SD) externalising	59.1 (10.5)	50.4 (9.9)	z=4.7, P<0.0001
Vineland adaptive behaviour scales—communication domain:			
Mean (SD) standard score	88.2 (15.2)	95.2 (9.8)	z=2.3, P=0.02
Mean (SD) age equivalent	7.8 (3.2)	9.1 (2.9)	z=2.7, P=0.006

*Results from χ^2 test or Mann-Whitney U test.
†Possible mental health disorder, or rate of psychiatric morbidity.
‡Social functioning below expected population norms.

Discussion

Most research on homeless people has focused on populations of single adults. This study highlights the high level of mental health needs among homeless children and their mothers. Homeless families constitute a relatively heterogenous population with complex health, social, and educational problems, which often precipitate the episode of homelessness. These are related to underlying psychosocial factors, and are likely to persist, even after rehousing.

The risk of mental health problems in children was not accounted for by socioeconomic deprivation, as they differed significantly from the comparison group on several measures. However, differences could be explained by confounding factors such as family and social stability (for example, there were fewer single parents in the comparison group). In contrast, residential, social, and family instability remained for a substantial proportion of homeless families, who thus re-entered a similar cycle of disruption. Residential instability was reflected in the percentage of families lost to follow up, as the local authority (housing, education, or social services) had no official record of them once they had moved from the first residence offered by the city council. Even after rehousing, children remained vulnerable to several risk factors, such as family breakdown, domestic violence, maternal mental health disorders, learning and developmental difficulties and delays, and loss of peer relationships.

These families do not fit into traditional public health and welfare systems.[20] There are no designated healthcare services for homeless families, and there is often little interagency coordination, with managers and policy makers often responding to different definitions of need and statutory obligations.[21] Some services have attempted to coordinate the care of homeless families and to provide support (and occasionally direct treatment) in a relatively structured way. Such projects include the provision of advocacy services, space for children to play and parents to meet, health visiting, input from general practitioners, social work, and input from community psychiatric nurses and community midwives.[3 22] The voluntary sector has also developed services covering hostels for homeless families. Although three major reports on the health and educational needs of homeless children and their families have been published in Britain,[3 6 23] few of their key recommendations have been implemented; if they have, this has been done in isolation, without setting up local or national standards.

Housing, education, health, and police services in each district need to establish a coordinating group to review the needs of homeless families, with the aim of developing and implementing a local strategy to facilitate rapid rehousing into permanent accommodation, effective social support and health care for parents and children, and protection from violence and intimidation. Central government and local housing authorities need a clear policy commitment to provide rapid and permanent rehousing for homeless families, to

Key messages

- Homeless children and their mothers have a high level of mental health problems
- Homeless families experience many risk factors, such as domestic violence, abuse, and family and social disruption
- In two fifths of children and a quarter of mothers, mental health problems persisted after rehousing
- In contrast with a comparison group of families of low socioeconomic status, a substantial proportion of homeless families remained residentially and socially unstable

minimise the risk of personal and family breakdown. New service models will require evaluation.

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Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study

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Editorial by Miller

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Whole cell vaccines against pertussis can induce a hypotonic-hyporesponsive episode or shock-like syndrome (collapse) in children,[1] but this may also occur with diphtheria and tetanus vaccines, acellular pertussis vaccine, and without vaccination.[2] Two prospective studies estimated that the rate of collapse after vaccination was considerable (13 out of 35 284 and 9 out of 15 752).[3 4] The only follow up study, which assessed a small series, was inconclusive about sequelae.[5]

Comparing the rates of collapse between countries poses problems because of differences in vaccination schedules and vaccines and in the way adverse reactions are monitored and symptoms reported. Moreover, case definitions are inconsistent.

Although the rate of recurrent collapse after whole cell pertussis vaccine has not been studied, for over 30 years repeat doses of vaccine have been contraindicated in children who experience a collapse reaction. Before 1993, in both the Netherlands and the United States children who had had a collapse reaction after vaccination with whole cell pertussis were not given a repeat dose. This contraindication still applies in the Netherlands, although most children are given further doses. We measured the numbers of cases of collapse in children after vaccination with whole cell pertussis vaccine in the Netherlands in 1994 and followed up all cases who were reported after their first dose.

Subjects, methods, and results

In the Netherlands over 99% of childhood vaccines are administered routinely by specialised staff within a child health clinic. All vaccinations are registered in provincial databases, so that data are accessible to medical staff if a child changes address. In 1962 an enhanced passive surveillance system for monitoring adverse events following vaccinations, with a 24 hour telephone service, was instigated. Some degree of underreporting is inevitable, but it seems to be limited and not biased against collapse (our laboratory's year report, 1994). Collapse is defined as sudden loss of muscle tone, pallor, and unresponsiveness. Sometimes symptoms are incomplete or atypical. When only one of the symptoms is present, the event is logged as an unspecified minor illness and not collapse.

In 1994, 712 adverse events were reported to the surveillance system, 587 after combined vaccination against diphtheria, tetanus, pertussis, and poliomyelitis (DTP-IPV vaccine) and *Haemophilus influenzae* type B (Hib-PRP-T vaccine). (The adverse events from *H influenzae* type B vaccine are infrequent and mild and not dealt with here.) After verification of symptoms we diagnosed 134 collapses (table).

In 1996 we followed up the 105 children with collapse reported after their first vaccinations. Detailed

Numbers of infants in the Netherlands with collapse reactions after vaccination against diphtheria, pertussis, tetanus, and poliomyelitis (DTP-IPV vaccine) with simultaneous *Haemophilus influenzae* type B vaccination (Hib-PRP-T vaccine)*

	Dose			
	First	Second	Third	Fourth
Scheduled age (months)	3	4	5	11
No who collapsed	105	19	7	3

*Birth cohort 200 000; vaccination uptake 97.5%.

information about subsequent vaccinations, health state, and development in 101 of the children was supplied by child health clinics. Four of the children were lost to follow up: two had moved abroad and the names of two were unknown. The parents of one child refused further vaccinations, and 16 children completed their schedule with the combined diphtheria, tetanus, and poliomyelitis vaccine (DT-IPV). The other 84 children received further pertussis vaccine (DTP-IPV), totalling 236 doses; 74 received the full three doses. None of the children had recurrent collapse, and other adverse events were only minor. No systematic precautions were taken, although about half the children were given paracetamol prophylactically for the second vaccination; most of them did not take it for subsequent doses. At the time of follow up the children's health and development showed no particular anomalies. One child who had not received further pertussis vaccinations developed severe pertussis.

Comment

The risk of recurrent collapse is higher than the background rate, which is low for second and subsequent vaccinations, but our data show that recurrence of collapse is exceptionally low (95% confidence interval 0% to 4.3%). A scheduled case-control study of all cases reported in 1995 would add to the numbers and contribute towards an understanding of risk factors and the effect of paracetamol used prophylactically.

Our preliminary results suggest that stopping further doses of pertussis vaccine is unneccessary and that vaccinations can still take place in a child healthcare clinic without special precautions. Parents, however, do need guidance and reassurance, and vaccination as an outpatient should be considered in the few cases in which parents' fears are not allayed.

We thank the staff of the child health clinics for providing us with the data.

Contributors: PEV-deB designed the study, assessed the adverse events, designed the follow up study, aquired and analysed the data, and wrote the manuscript; she will act as guarantor of the study. JL designed the study, took part in the surveillance scheme, investigated reports, and helped write the manuscript. HCR designed the study, took part in the surveillance scheme, investigated reports, and helped write the manuscript.

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Phantom pain, anxiety, depression, and their relation in consecutive patients with amputated limbs: case reports

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Parkes suggested that emotional factors are influential in patients' experience of prolonged pain in a phantom limb after amputation and concluded that this may be prevented if patients are encouraged to express grief over their loss.[1] However, Katz and Melzack found no significant difference in standardised tests of psychological dysfunction between patients who experienced phantom pain and those who did not. They concluded that the pain is more likely to vary with the experience of preamputation pain, even retaining many of its characteristics.[2] A review of the literature on measures used to diagnose psychopathology found that many measures include items that confound emotional distress with the physical disorder and thus overestimate it.[3] We investigated whether people who had had arms or legs amputated experienced emotional distress, and the relation between the distress and pain, using standardised screening techniques designed for patients with physical illness.

Patients, methods, and results

Calculations of sample size indicated that 21 patients per group would be needed to show a reliable difference at the 5% level of significance. The participants were 93 consecutive patients who had been referred to the prosthetic rehabilitation clinic and were aged 34-91 (mean 65) years; 54 were men. Time since amputation was 1-58 (9.7) years. Sixty patients had had a leg amputated for vascular illness, including diabetes, 10 of them losing both legs. Twenty four patients had lost a leg and nine an arm because of trauma. RSH obtained a clinical history including information about previous and concurrent medical and psychiatric problems. Phantom pain was assessed with the short form McGill pain questionnaire,[4] the patients endorsing all words describing their phantom pain, if present. KF, who was blind to the pain report, then assessed them with the hospital anxiety and depression scale.[5]

Table 1 Differences between patients with and without pain in phantom limb in time from amputation and scores on hospital anxiety and depression scale. Values are means (95% confidence intervals)

	Phantom pain (n=29)	Non-phantom pain (n=64)	Correlation	
			Mann-Whitney U test	Kendall's tau*
Time from amputation (years)	6.79 (2.62 to 10.96)	11.06 (7.14 to 14.98)	873, P=0.65	
Anxiety score	4.66 (2.74 to 6.66)	3.59 (3.38 to 3.80)	912, P=0.90	0.16, P=0.03
Depression score	3.45 (1.82 to 5.08)	2.78 (2.09 to 3.47)	892, P=0.76	−0.04, P=0.53

* For time from amputation.

Phantom pain (mostly mild) was reported by 29 patients. Fifty three of the remaining 64 patients reported non-painful sensations in the phantom limb. Mean scores on the anxiety and depression scale were 3.9 for anxiety and 2.9 for depression. Whereas 10 patients scored in the clinical range for anxiety, mainly about falling, only one patient scored in this range for depression. No patient gave a history of previous or concurrent psychiatric treatment.

The patients were divided according to whether they experienced pain, and their anxiety and depression scores and time from amputation were compared with non-parametric statistics. The table shows that the time from amputation, and anxiety and depression scores did not differ between the two groups. Time from amputation was not strongly significantly associated with distress, so anxiety and depression do not seem to vary consistently over time.

Comment

The incidence of phantom pain in this study was 31%, in keeping with current reports.[2] Only a few patients experienced emotional distress, anxiety being reported more often than depression. The prevalence of depression was low, suggesting that it is an uncommon reaction to amputation. In this elderly group of patients who had discomfort due to vascular illness, loss of the limb did not constitute a bereavement in the way that Parkes suggested.[1]

These results, in agreement with those of Katz and Melzack,[2] show little support for the grief hypothesis, since it is difficult to sustain a concept of grief in the absence of depression on objective measures. In addition, we found no relation between the experience of pain and emotional distress, suggesting that phantom pain is not a function of emotional adjustment.

Dr M J Campbell and Dr Robert West commented on the statistics.

Contributors: RSH undertook the initial assessment of the patients and administered the McGill pain questionnaire. KF administered the hospital anxiety and depression scale, analysed the data, and wrote the paper. KF is the guarantor for the study.

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Conflict of interest: None.

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Influence of travel patterns on mortality from injury among teenagers in England and Wales, 1985-95: trend analysis

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Injuries are the leading cause of death among teenagers.[1] The Health of the Nation strategy aims to reduce mortality from accidents in young people by 25% by 2005.[2] We previously analysed how changing travel patterns influenced death rates from unintentional injury among children under 14 years of age.[3] Here we examine how they affect mortality from unintentional injury among teenagers.

Subjects, methods, and results

From the Office for National Statistics we obtained anonymised death certificates recording deaths from injury between 1985 and 1995 among people aged 15-19 years in England and Wales. Records included age, sex, external cause of injury (E code), and year of death. We defined deaths of road users by E codes (table) and calculated mortality using census data and the average distance travelled as denominators. Data on the average annual distances travelled were obtained from the national travel surveys, whose methods have been published.[4] We analysed unpublished data from the 1985-6, 1989-91, and 1992-4 surveys for residents of England or Wales aged 15-19 (Department of Transport, 1996). We estimated the average distance travelled by car, motorcycle, bicycle, and foot each year, from travel survey midpoints using linear regression.[3] We estimated trends using Poisson distribution.[5]

Between 1985 and 1995, 10 530 teenagers aged 15-19 died from injury in England and Wales; 7954 deaths were from unintentional injury, of which 6073 (76%) involved road users (table). Mortality from unintentional injury declined by 32% (95% confidence interval −37% to −27%) over this period. There were large declines in death rates for motorcyclists (−78%; −81% to −74%), pedestrians (−49%; −59% to

Death rates and numbers of deaths from road use among teenagers aged 15-19 in England and Wales by sex, with cumulative changes in death rates, 1985-95

	Motorcyclist*		Pedestrian†		Pedal cyclist‡		Car occupant§	
Year	Male	Female	Male	Female	Male	Female	Male	Female
Death rate per 100 000 population (No of deaths)								
1985	12.1 (246)	1.4 (27)	3.2 (65)	1.8 (35)	1.7 (35)	0.4 (7)	10.1 (206)	3.7 (71)
1986	11.8 (236)	1.1 (21)	4.1 (83)	2.0 (39)	1.2 (25)	0.3 (6)	12.2 (244)	5.4 (103)
1987	11.0 (216)	0.9 (17)	3.3 (64)	1.8 (33)	1.7 (33)	0.3 (6)	13.1 (256)	4.3 (81)
1988	8.9 (169)	0.9 (16)	2.9 (56)	1.3 (24)	1.4 (26)	0.0 (0)	12.0 (229)	4.6 (84)
1989	8.5 (155)	1.0 (17)	3.6 (65)	1.9 (33)	1.8 (33)	0.2 (3)	15.7 (287)	6.3 (109)
1990	8.5 (150)	0.9 (15)	1.9 (34)	1.5 (25)	1.7 (30)	0.2 (4)	16.2 (285)	5.8 (97)
1991	6.3 (105)	0.7 (11)	2.7 (45)	1.7 (27)	1.4 (23)	0.3 (5)	13.0 (217)	4.7 (74)
1992	4.4 (71)	0.7 (10)	2.0 (32)	1.3 (19)	1.6 (25)	0.1 (1)	13.3 (213)	4.6 (70)
1993	3.0 (47)	0.2 (3)	2.2 (34)	1.3 (19)	0.6 (10)	0.3 (4)	10.4 (160)	3.9 (57)
1994	3.1 (48)	0.3 (4)	1.7 (26)	1.5 (22)	1.0 (16)	0.1 (2)	11.2 (172)	4.6 (66)
1995	2.5 (39)	0.0 (0)	2.1 (32)	0.6 (9)	1.1 (17)	0.1 (2)	11.4 (174)	4.2 (61)
1985-95	7.6 (1482)	0.8 (141)	2.8 (536)	1.6 (285)	1.4 (273)	0.2 (40)	12.6 (2443)	4.8 (873)
Percentage change in death rate (95% CI)								
1985-95	–78 (–81 to –73)	–81 (–90 to –67)	–51 (–63 to –35)	–44 (–62 to –17)	–35 (–56 to –5)	–53 (–83 to 32)	–1 (–13 to 12)	–4 (–23 to 19)
Percentage change in No of deaths/km (95% CI)								
1985-95	–31 (–42 to–17)	N/A	–39 (–54 to –20)	–22 (–47 to 14)	–16 (–43 to 23)	10 (–62 to 209)	–30 (–38 to –20)	–25 (–40 to –7)

*E810-819 ending in .2 or .3.†E810-819 ending in .7. ‡E810-819 ending in .6, and E826. §E810-819 except ending in .2, .3, .6, or .7.
N/A=annual distance travelled insufficient to calculate reliable trend estimates for deaths per km travelled.

− 36%), and pedal cyclists (− 38%; − 57% to − 11%), but not car occupants (− 2%; − 12% to 9%).

Young men accounted for 6279 (79%) deaths from unintentional injury, and young women for 21% (1675). The sex ratio varied by road user (table). Declines in mortality of motorcyclists, pedestrians, and car occupants were similar for men and women. The decline in death rates of cyclists was larger among women, although the point estimates are not very precise.

The average annual distance travelled by motorcycle declined by 78%, from 246 km to 54 km, the average annual distance walked fell by 24%, from 624 km to 472 km, and the average annual distance cycled fell by 31%, from 216 km to 149 km. The average annual distance travelled by car increased by 35%, from 4510 km to 6069 km. Declines in motorcycling (− 99%), walking (− 28%), and cycling (− 60%) were larger and the increase in car travel smaller (28%), in young women than they were in young men (− 73%, − 20%, − 24%, and 40%, respectively).

In 1995 mortality was lowest for people travelling by car (1.3 deaths/100 million km travelled). Overall, 2.9 pedestrians, 4.3 cyclists, and 23.9 motorcyclists died per 100 million km travelled. Cumulative declines in deaths per 100 000 population (see above) were larger than declines in deaths per km travelled for motorcyclists (− 20%; − 33% to − 5%), pedestrians (− 33%; − 46% to − 16%), and cyclists (− 10%; − 37% to 29%). Deaths per km travelled by car declined substantially (− 27%; − 35% to − 19%), unlike deaths of car occupants per 100 000 population. Deaths per km declined more for young men than for young women in each road user group (table).

Comment

The 32% decline in mortality from unintentional injury among people aged 15-19 since 1985 is largely due to falling mortality among motorcyclists, pedestrians, and cyclists. These declines correspond to large decreases in motorcycling, walking and cycling. Mortality among car occupants has not declined, despite a 27% decrease in deaths per km travelled by car, because of the large increases in the distance travelled by car. Transport patterns are an important determinant of adolescent health. Strategies to influence transport patterns could substantially reduce mortality from road crashes.

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Conflict of interest: None.

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Endpiece

What's a network?

Network: Any thing reticulated or decussated, at equal distances, with interstices between the intersections.

Samuel Johnson, *Dictionary of the English Language* (1755)