tions. We know next to nothing, for example, about the predictors of major bleeding on warfarin, or the characteristics that make it likely that the benefits of endarterectomy will outweigh the risks in a patient with asymptomatic carotid stenosis.

The lack of basic clinical research on the issues that matter most to patients and practising clinicians inevitably calls into question whether medical academia, as currently constituted and funded, is properly fit for purpose. Basic biological research and bench-to-bedside translation are obviously important, but why has so much critically important basic clinical research not been done? Whatever the causes (some possible ones are given in the box), medical academia must improve its performance or, less preferably, be forced by politicians to prioritise appropriately. The recent emphasis on the development of clinical research is welcome,[2] as are the recent UK Department of Health proposals for future research funding,[11] although there are potential pitfalls.[12] Greatest of these is the tendency for clinical research to be defined too narrowly as being only bench-to-bedside translational research, large scale epidemiology, and pharmaceutical trials, with the lowest hanging fruit—observational research necessary for effective clinical practice—continuing to be neglected.

Peter M Rothwell *professor of clinical neurology*

(peter.rothwell@clneuro.ox.ac.uk)

Stroke Prevention Research Unit, University Department of Clinical Neurology, Radcliffe Infirmary, Oxford OX2 6HE

Competing interests: None declared.

1 McNally N, Kerrison S, Pollock AM. Reforming clinical research and development in England. *BMJ* 2003;327:550-3.
2 Academy of Medical Sciences. *Strengthening clinical research*. London: Academy of Medical Sciences, 2003. www.acmedsci.ac.uk (accessed 7 April 2006).
3 Whiting P, Harbord R, Main C, Deeks JJ, Filippini G, Egger M, Sterne JAC. The accuracy of MRI for the diagnosis of MS: as systematic review. *BMJ* 2006;332:875-8.
4 Evangelou N, Rothwell PM. A systematic review of brain MRI in the diagnosis of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1997;63:262-3.
5 Rothwell PM. Lack of epidemiological data on secondary stroke prevention. *Lancet Neurology* 2005;4:518-9.
6 Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;284:2901-6.
7 Coull A, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Early risk of stroke after a TIA or minor stroke in a population-based incidence study. *BMJ* 2004;328:326-8.
8 Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JNE, Warlow CP, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after a transient ischaemic attack. *Lancet* 2005;366:29-36.
9 Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006;367:397-403.
10 Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77:193-8.
11 Department of Health. Best research for best health: a new national health research strategy. 2005: www.dh.gov.uk/PublicationsAndStatistics/Publications (accessed 7 April 2006).
12 Warlow C. A new NHS research strategy. *Lancet* 2006;367:12-3.

Brains and mobile phones

The biggest risk to health from mobile phones is using them while driving

Research pp 883, 886

There are more than 50 million mobile phones in the United Kingdom, and more than 1 billion worldwide. Mobile phones allow people to communicate with flexibility and ease. In addition, having a personal and mobile means of communication has helped to save lives through quicker notification of accidents, trauma, and other dangers.[1] But concerns about the safety of mobile phones have been raised.

In 2000 the UK Independent Expert Group on Mobile Phones (IEGMP) published the Stewart report.[2] The report recommended a programme of research and a precautionary approach to the use of mobile phones, especially use by children. As a result of the recommendations a research programme was launched in 2001 with a budget of £7.36m (€10.5m; $13m), jointly funded by government and industry. Two papers in this week's *BMJ* come out of this initiative.[3 4]

Hepworth and colleagues (p 883) conducted a population based case-control study of 966 patients with gliomas and found that use of mobile phones, in the short and medium term, is not associated with increased risk of developing a glioma.[3] The response rate of only 51% in this study, predominantly from patients with low grade tumours, may contribute to missing a real but small effect. The study illustrates the difficulty of estimating use of mobile phones over many years and with different technology (analogue and digital), and thus the uncertainty in estimating exposure to radiofrequency radiation.

As there is no obvious biological mechanism for cancer to be caused by radiofrequency radiation, there is probably no relation between mobile phone use and development of gliomas. But the latency period for formation of gliomas could be longer than the period studied by Hepworth and colleagues, and longer surveillance will be necessary to reach more reliable conclusions. Greenfield's neuropathology textbook states: "Such an association [between radiofrequency radiation from mobile phones and malignant gliomas] would be surprising given the short time since the introduction of the widespread use of mobile phones: in adult humans, all known environmental carcinogens, including radiation, require a latency period of usually more than 20 and often more than 30 years."[5] In Hepworth and colleagues' study only a small number of participants with glioma reported exposure of more than 10 years.

Some evidence indicates, however, that acoustic neuromas and salivary tumours may be related to use of mobile phones. Hepworth and colleagues' paper derives from an international collaborative study on use of mobile phones and risks of intracranial tumours, and perhaps these associations will also be studied.

Also in this week's *BMJ* (p 886) Rubin and colleagues examine the phenomenon of "electromagnetic hypersensitivity."[4] This is a collection of

BMJ 2006;332:864–5

symptoms such as headache, nausea, fatigue, dizziness, and loss of memory or concentration apparently precipitated by exposure to electromagnetic radiation. In Sweden it is accepted as a physical impairment, and a national scheme exists to improve home and work conditions for sufferers.

Rubin and colleagues conducted a double blind randomised within participants provocation study in a group of people who reported sensitivity to electromagnetic fields. The study failed to show that symptoms were associated with exposure to mobile phone radiation. People in the sensitive group had more severe symptoms (compared to controls), but their symptoms of electromagnetic hypersensitivity occurred with the same frequency when the mobile phone was switched on and during sham exposure. The authors describe this as a nocebo phenomenon, and suggest the role of psychological factors.

The IEGMP accepted that mobile phone radiation may produce biological effects, but it did not think that such radiation caused adverse health effects. In 2005 the National Radiological Protection Board updated the Stewart report and proposed that this conclusion still holds true.[6] Hepworth's paper gives some further reassurance but, as the Global System for Mobile Communications (GSM) is now barely 10 years old, the question remains whether this technology has been in use for a sufficient period to allow recognition of an effect of exposure on the development of brain pathology. Rubin's study shows that some people develop symptoms to expected exposures even in the absence of such exposure. This finding does not necessarily preclude a real effect.

The evidence to date suggests that any risk to the individual mobile phone user of developing brain pathology is fleetingly small. The Health Council of the Netherlands even states that there is no reason to recommend that mobile phone use by children should be limited, and no need to apply the precautionary principle.[7]

The most important established risk of mobile phones to people is their use while driving. This is true for hand held phones as well as for hands free ones. Since 2003 it has been illegal in the United Kingdom to drive a car while using a hand held phone, but still legal to use a hands free one. It is time to correct this discrepancy.

Michael Maier *senior clinical lecturer*

(michael.maier@imperial.ac.uk)

Division of Neuroscience and Mental Health, Charing Cross Campus, Imperial College, London W6 8RP

Competing interests: None declared.

1 Chapman S, Schofield WN. Emergency use of cellular (mobile) telephones. *Lancet* 1998;351:650.
2 Independent Expert Group on Mobile Phones. *Report of the Group (The Stewart Report)*. 2000. www.iegmp.org.uk/report/index.htm (accessed 1 Apr 2006).
3 Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren MJA, McKinney PA. Mobile phone use and risk of glioma in adults: case-control study. *BMJ* 2006:332:883-6.
4 Rubin GJ, Hahn G, Everitt BS, Cleare AJ, Wessely S. Are some people sensitive to mobile phone signals? Within participants double blind randomised provocation study. *BMJ* 2006:332:886-9.
5 Graham DI, Lantos PL. *Greenfield's neuropathology*. 7th ed. London: Arnold, 2002.
6 National Radiological Protection Board. Mobile Phones and Health 2004: Report by the NRPB. Didcot: NRPB, 2005. www.hpa.org.uk/radiation/publications/documents_of_nrpb/pdfs/doc_15_5.pdf (accessed 31 Mar 2006).
7 Health Council of the Netherlands. *Mobile telephones: an evaluation of health effects*. 2002. www.gr.nl/pdf.php?ID=377&p=1 (accessed 31 Mar 2006).

Strict glucose control in the critically ill

May not be such a good thing for all critically ill patients

In 2001 Van den Berghe et al reported the results of a randomised controlled trial comparing the mortality of critically ill surgical patients receiving insulin infusions to achieve "tight glycaemic control" (target blood glucose 4.4-6.1 mmol/l) with that of patients receiving conventional treatment, where insulin was infused only if the blood glucose exceeded 11.9 mmol/l and was adjusted to maintain values of 10-11.1 mmol/l.[1] The trial was stopped after 1548 patients had been enrolled because the mortality in the tight control group was 4.6% compared with 8% in the control group (32% corrected relative reduction; P = 0.04). Ever since, tight glycaemic control has been standard practice, but there are now good reasons to question it.

It always seemed surprising that a simple change in blood glucose management reduced mortality more than other far more costly and complex interventions tested through randomised trials in the critically ill. The only corroborating evidence came from studies of glucose-insulin-potassium treatment in acute myocardial infarction outside a critical care setting[2] and an observational study of tight glycaemic control in a general intensive care setting.[3] The 2001 study was conducted on a relatively restricted population consisting mainly of post-surgical patients (63% after cardiac surgery) with low admission APACHE II scores and used an unusual feeding regimen. In spite of these limitations, tight glycaemic control rapidly became standard practice in critically ill medical as well as surgical patients in Britain[4] and an internationally recommended standard of care in all patients with severe sepsis.[5]

However, confidence in the benefits of strict glucose control for all critically ill patients is being eroded. Last year the German SepNet group suspended a multicentre randomised controlled trial in medical and surgical patients with severe sepsis.[6] Tight glycaemic control produced no reduction in mortality, but it did cause a higher incidence of hypoglycaemia (12.1% *v* 2.1%). Also last year the CREATE-ECLA trial, a study of insulin-glucose-potassium therapy in 20 000 patients with acute myocardial infarction,[7] showed no benefits, removing some of the indirect support for tight glycaemic control. Finally, early this year Van den Berghe and colleagues reported another study of tight glycaemic

BMJ 2006;332:865–6

Cite this article as: BMJ, doi:10.1136/bmj.38720.687975.55 (published 20 January 2006)

Research

Mobile phone use and risk of glioma in adults: case-control study

Sarah J Hepworth, Minouk J Schoemaker, Kenneth R Muir, Anthony J Swerdlow, Martie J A van Tongeren, Patricia A McKinney

Abstract

Objective To investigate the risk of glioma in adults in relation to mobile phone use.
Design Population based case-control study with collection of personal interview data.
Setting Five areas of the United Kingdom.
Participants 966 people aged 18 to 69 years diagnosed with a glioma from 1 December 2000 to 29 February 2004 and 1716 controls randomly selected from general practitioner lists.
Main outcome measures Odds ratios for risk of glioma in relation to mobile phone use.
Results The overall odds ratio for regular phone use was 0.94 (95% confidence interval 0.78 to 1.13). There was no relation for risk of glioma and time since first use, lifetime years of use, and cumulative number of calls and hours of use. A significant excess risk for reported phone use ipsilateral to the tumour (1.24, 1.02 to 1.52) was paralleled by a significant reduction in risk (0.75, 0.61 to 0.93) for contralateral use.
Conclusions Use of a mobile phone, either in the short or medium term, is not associated with an increased risk of glioma. This is consistent with most but not all published studies. The complementary positive and negative risks associated with ipsilateral and contralateral use of the phone in relation to the side of the tumour might be due to recall bias.

Introduction

Gliomas are the most common malignancy of the central nervous system in adults, and the prognosis is extremely poor.[1] The distinct histopathology and cellular origin of gliomas are probably associated with different aetiological pathways and mechanisms of carcinogenesis than other subtypes of brain tumours; the aetiology of gliomas, however, remains unclear. Recently, considerable interest has focused on whether the use of mobile phones is associated with an increased risk of gliomas and other brain tumours, even though little is known about potential mechanisms.[2] The energy of the radiofrequency fields emitted by mobile phones is thought to be insufficient to cause malignant transformation through direct damage to DNA.[3]

Most published epidemiological studies on mobile phone use and gliomas have not generally reported any increased risk either overall or with long term use.[4–7] Individual studies have found positive associations between high grade astrocytoma (glioma) and phone use ipsilateral to the side of the tumour,[8] brain tumours and phone use in rural areas,[9] and use of analogue mobile phones.[8 10]

We carried out a large population based case-control study of 966 patients with glioma in the United Kingdom. This study is part of the Interphone project,[11] an international collaboration of 13 countries investigating mobile phone use and the risk of intracranial tumours.

Methods and participants

The study took place in the Thames regions of south east England and four areas to the north (Trent, West Midlands, West Yorkshire, and southern Scotland). The total catchment population (28.4 million) comprised 48.3% of the UK population. All areas followed a common protocol, with identical methods of case ascertainment and data collection with controls randomly sampled from general practitioner lists. The south east slightly differed in its method of control selection and the age range covered.

Cases were ascertained from multiple sources, including hospital departments (neurosurgery, neuro-oncology, neuropathology, neuroradiology, neurology) and cancer registries. Patients aged 18-69 years (northern centres) or 18-59 years (south east) lived in the study areas and had a first diagnosis between 1 December 2000 and 30 June 2003 (northern) or 29 February 2004 (south east) with a glioma (ICD-O-3 (international classification of diseases for oncology)[12] topography: C71, morphology: 9380-9411, 9420-9460, 9480, 9505). Data on site, laterality (left, right, central) and grade of tumour (WHO grade high III-IV; low I-II[13]) were abstracted from scan and pathology reports.

In the most recent year we have published data for (1992) an estimated 98% of the UK population was registered with a general practitioner.[14] Controls were randomly selected from general practitioners' lists by a preset algorithm. In the south east the controls were frequency matched to reflect the age, sex, and geographical distribution of cases. In the northern centres one control per case was individually matched on age, sex, and general practice after the patient with glioma was interviewed. Non-participating controls were replaced. Parallel case-control studies of meningioma, acoustic neuroma, and other brain tumours were carried out with identical methods and questionnaires; the controls for these cases were included in the present analyses.

Consultants or general practitioners approached eligible participants personally or by an invitation letter. The study was introduced as an investigation of risk factors for brain tumours, without emphasising mobile phones. With the participant's informed consent, trained interviewers conducted a computer assisted personal interview. For 69 patients with glioma (7%), interviewers conducted proxy interviews, mainly with spouses.

During the interview, if participants reported that they had ever made one or more calls each week on average for a period of six months or longer, they were asked a detailed set of questions on mobile phone use. For such participants, all makes and models of phone were recorded, with a comprehensive rep-

ertoire of photographs to prompt recall. For each phone, the interviewer recorded the network operator, start and stop year, and the number and duration of calls made and received. If participants were uncertain about the calendar years or amount of use, a range was reported with the mean value taken for analysis. Additional details were gathered on which side of the head the phone was mostly used (50% or more of the time) and factors influencing emitted power levels to the head, including use of hands-free kits (start and stop dates of use and proportion of time used) and whether the phone was used mainly in an urban or rural area or equally in both.[15]

In the analysis, we defined regular phone use as use for at least six months in the period more than a year before diagnosis. We defined diagnostic date as the date of diagnostic pathology (n=935, 97%) or date of the first diagnostic scan (n=31, 3%) if diagnostic pathology was unavailable. We assessed exposure to mobile phones using the number of years from first regular use of a phone until diagnosis or equivalent reference date for controls, lifetime years of regular use, lifetime cumulative use (hours), and lifetime cumulative number of calls. Long term users (>10 years) were dichotomised into heavy (≥113 hours) and light (<113 hours) cumulative hours of use in the period 10 or more years before diagnosis, with the cut off point based on the median hours of use among control participants. We used data collated by Interphone[11] to classify phones as either analogue or digital, based on make and model of phone, year of use, and network operator capabilities during that period.

The exposure period for people with glioma was calculated up to a year before the date of diagnosis. An equivalent reference date was required for control participants that allowed for the increase in mobile phone use over the study period and as controls tended to be interviewed after the patients with glioma. For each area (south east, northern), we constructed case strata by single calendar year of interview and single year interval between diagnosis and interview ("interview lag time"). Control participants interviewed in each calendar year were randomly allocated to strata of interview lag time, proportionally to the distribution of the cases in the same calendar year, to obtain a similar distribution of lag time as in the cases. We then calculated the reference dates for controls by subtracting the mean interview lag time in cases in that stratum from the interview dates of the controls. Exposure indices were calculated up to a year before this reference date for controls (that is, a one year latency time was used). Additional analyses were carried out with a five year latency time.

Statistical analysis

For statistical analysis we used unconditional logistic regression (StataCorp, College Station, TX) adjusted for nine regions (five regions within the south east and the four northern regions), age at reference date (five year categories), sex, deprivation (Townsend score[16]), and combinations of interview year and lag time to account for the fact that controls were, on average, interviewed later in the study period than patients with glioma. We derived odds ratios for cumulative use with and without modification for reported use of headsets or hands-free sets in a vehicle, or both,[7 17] with and without proxy case interviews, and separately for high and low grade tumours and urban versus rural use. We also performed a conditional logistic regression analysis on the matched northern case-control dataset.

We used two methods to assess the risk of a tumour ipsilateral or contralateral to side of phone use. Firstly, we took two groups of patients with right and left sided tumours[17] and randomly assigned controls to each group and considered them to have a tumour on that side (50% left, 50% right) for the analysis. The odds ratio for risk of an ipsilateral tumour was based on the results of a logistic regression analysis where ipsilateral phone use was use on the same side of the head as the tumour for cases or the assigned side for controls. We adjusted the analysis for the side of the tumour as well as the variables adjusted for in the main analysis. If the phone was used on the opposite side to the side of tumour/allocated side the participant was classified as unexposed. Those who reported using the phone on both sides of the head were considered exposed on both the left and right sides.[6 17] As the allocation of controls was based on a random assignment, the logistic regression analysis was repeated 500 times; the results for the analysis that gave the median odds ratio for ipsilateral regular phone use are presented. A similar analysis of contralateral use (use on the opposite side of the head to the tumour or allocated side) was performed. The second method calculates a relative risk for laterality of reported side of use in relation to tumour laterality but only in cases.[4]

Results

Researchers interviewed 966 cases (367 in the south east and 599 in northern areas) and 1716 controls (630 and 1086). The main reasons for non-participation were the participant was too ill or had died before interview (cases 30%, controls <1%), non-response (cases 2%, controls 21%), refusal (cases 10%, controls 29%), and other reasons (refusal by consultant or general practitioner, non-English speaking, mental impairment) (cases 7%, controls 5%). Non-responders included those for whom contact details may have been incorrect. Overall response rates were 51% for patients with glioma and 45% for controls, representing the proportion of all eligible cases and controls from the study areas who were interviewed in the study. Exclusion of the non-responders (that is, who may never actually have been asked) gave response rates of 51% and 57%. Interviewed patients with glioma were broadly representative of the overall set of those eligible by age and sex but differed by deprivation category, being significantly more affluent (χ^2 test for trend, $P<0.001$). People with low grade glioma were significantly more likely to be interviewed (χ^2 test, $P<0.001$) than those with high grade glioma. For control participants, those interviewed were more likely to be women (χ^2 test, $P<0.001$) and more likely to be affluent (χ^2 test for trend, $P<0.001$) than those who were not interviewed.

Table 1 shows the demographic distribution of interviewed cases and controls. The proportion of men was higher among the patients with glioma than in the control group. There was also a slight tendency for interviewed controls to live in more affluent areas than interviewed patients with glioma.

Table 2 shows an odds ratio of 0.94 (95% confidence interval 0.78 to 1.13) for regular phone users compared with those who never or only occasionally used mobile phones. There was no association of risk with lifetime years of use, cumulative hours of use, cumulative numbers of calls, nor cumulative hours of use over 10 years before the reference date. These findings were similar after we excluded patients with glioma with proxy interviews (n=69), adjusted cumulative hours of phone use and number of calls for use of hands-free kits, applied a five year lag time, or restricted analysis to matched case-control analysis of northern cases. Table 2 also shows no significant associations with use in urban or rural areas or separately for 650 high grade and 306 low grade gliomas.

We found a significant odds ratio of 1.24 (1.02 to 1.52) for a tumour ipsilateral to side of phone use and a reduced odds ratio

Table 1 Demographic distributions in cases and controls. Figures are numbers (percentages) of participants

	Cases (n=966)	Controls (n=1716)
Region:		
Thames regions	367 (38.0)	630 (36.7)
Southern Scotland	152 (15.7)	277 (16.1)
Trent	199 (20.6)	372 (21.7)
West Midlands	115 (11.9)	207 (12.1)
West Yorkshire	133 (13.8)	230 (13.4)
Age at reference date (years):		
18-29	100 (10.4)	112 (6.5)
30-39	199 (20.6)	281 (16.4)
40-49	216 (22.4)	429 (25.0)
50-59	328 (34.0)	645 (37.6)
60-69†	123 (12.7)	249 (14.5)
Men	604 (62.5)	829 (48.3)
Women	362 (37.5)	887 (51.7)
Deprivation score*:		
1 (most affluent)	257 (26.6)	513 (29.9)
2	229 (23.7)	386 (22.5)
3	178 (18.4)	334 (19.5)
4	181 (18.7)	292 (17.0)
5 (least affluent)	121 (12.5)	191 (11.1)

*Townsend score (area based measure of deprivation) categorised into five equally sized groups based on 2001 census data.
†In control group includes seven people aged >69 at reference date.

for contralateral use (0.75, 0.61 to 0.93) (table 2). Similar respective excesses and deficits were present for all exposure measures of mobile phone use, including use for ≥10 years (ipsilateral 1.60, 0.92 to 2.76; contralateral 0.78, 0.43 to 1.41). To investigate this further, we analysed regular use ipsilateral and contralateral to handedness, which gave odds ratios of 0.78 (0.62 to 0.99) and 1.07 (0.85 to 1.35), respectively. The concordance between reported side of use and handedness was 59% for cases and 64% among controls. The method of Inskip et al[4] gave an overall relative risk of 1.3 (Fisher's exact $P < 0.001$) for a tumour ipsilateral to the side of phone use.

We examined use of analogue phones separately but there were no significant odds ratios with any exposure metric (table 3). Results from the conditional regression analysis of matched data from the northern centres did not differ from the overall findings.

Discussion

This large study on associations between mobile phone use and the risk of developing a glioma in a UK population has nearly twice as many cases as the largest previously reported studies of gliomas,[4 5] with more long term users. In addition, it was designed specifically to address exposure to mobile phones, with comprehensive and relevant collection of data. Overall, we found no raised risk of glioma associated with regular mobile phone use and no association with time since first use, lifetime years of use, cumulative hours of use, or number of calls. Our results are consistent with findings from investigations of mobile phone use in the US,[4 5] Denmark,[7 18] and Sweden,[6] though some studies have found isolated positive associations for particular variables.[8–10]

Analogue phones emit higher average power levels than digital phones.[19] If mobile phone use was causally linked to the development of glioma and risk was related to power level, we would predict a higher risk for analogue phone use than for digital phones. As in some[6 7 18] but not all[8 10] previous reports we found no association between risk of glioma and use of analogue

Table 2 Odds ratios and 95% confidence intervals for risk of glioma in relation to mobile phone exposure*. Figures are numbers (percentages) of participants

Factor and level of exposure	Cases (n=966)	Controls (n=1716)	Odds ratio† (95% CI)
Frequency of use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
Regular	508 (52.6)	898 (52.3)	0.94 (0.78 to 1.13)
Not known	2 (0.2)	0	—
Years since first use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
1.5-4‡	271 (28.1)	515 (30.0)	0.90 (0.73 to 1.11)
5-9	170 (17.6)	270 (15.7)	1.04 (0.80 to 1.34)
≥10	66 (6.8)	112 (6.5)	0.90 (0.63 to 1.28)
Not known	3 (0.3)	1 (0.1)	—
Lifetime years of use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
0.5-4	342 (35.4)	623 (36.3)	0.93 (0.76 to 1.14)
5-9	115 (11.9)	206 (12.0)	0.88 (0.66 to 1.17)
≥10	48 (5.0)	67 (3.9)	1.14 (0.74 to 1.73)
Not known	5 (0.5)	2 (0.1)	—
Cumulative hours of use§:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
≤99	225 (23.3)	444 (25.9)	0.94 (0.76 to 1.17)
99-≤544	128 (13.3)	218 (12.7)	0.87 (0.65 to 1.15)
>544	135 (14.0)	217 (12.6)	0.94 (0.71 to 1.23)
Not known	22 (2.3)	19 (1.1)	—
Cumulative number of calls§:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
≤2071	237 (24.7)	444 (25.9)	0.99 (0.80 to 1.23)
2071-≤6909	102 (10.6)	217 (12.6)	0.70 (0.52 to 0.93)
>6909	146 (15.1)	218 (12.7)	0.97 (0.74 to 1.28)
Not known	25 (2.6)	19 (1.1)	—
Cumulative hours of use ≥10 years ago¶:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
<10 years	429 (44.4)	772 (45.0)	0.93 (0.77 to 1.13)
≥10 years, ≤113 hours	23 (2.4)	56 (3.3)	0.61 (0.36 to 1.04)
≥10 years, >113 hours	39 (4.0)	54 (3.2)	1.11 (0.70 to 1.75)
Not known	19 (2.0)	16 (1.0)	—
Proportion urban/rural at first use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.00
Mainly urban	241 (24.9)	471 (27.4)	0.83 (0.66 to 1.03)
Mainly rural	49 (5.1)	84 (4.9)	0.98 (0.66 to 1.46)
Both	215 (22.3)	343 (20.0)	1.05 (0.83 to 1.31)
Not known	5 (0.5)	0	—
According to tumour grade**			
Frequency of use in those with high grade tumours:			
Never/non-regular	331 (50.9)	818 (47.7)	1.00
Regular	317 (48.8)	898 (52.3)	0.95 (0.77 to 1.17)
Not known	2 (0.3)	0	—
Frequency of use in those with low grade tumours:			
Never/non-regular	122 (39.9)	818 (47.7)	1.00
Regular	184 (60.1)	898 (52.3)	0.85 (0.63 to 1.13)
Not known	0	0	—
According to side of phone use††			
Frequency of ipsilateral use*:			
Never/non-regular	550 (66.3)	1230 (71.7)	1.00
Regular	278 (33.5)	486 (28.3)	1.24 (1.02 to 1.52)
Not known	2 (0.2)	0	—
Frequency of contralateral use*:			
Never/non-regular	629 (75.8)	1225 (71.4)	1.00
Regular	199 (24.0)	491 (28.6)	0.75 (0.61 to 0.93)
Not known	2 (0.2)	0	—

*Reference category is never or non-regular use of any type of mobile phone and, in ipsilateral analysis, phone use only on opposite side of tumour, and in contralateral analysis, phone use only on same side as tumour.
†Odds ratios adjusted for age at reference date (in 5 year age groups), sex, region, Townsend deprivation category, and interview reference date category.

‡Lower limit 1.5 years ago because regular phone use defined as phone use of at least six months' duration at least one year before reference date.
§For cumulative number and duration of calls category cut-off points were median and 75th centile of use for controls who were regular phone users.
¶Use over 10 years before reference date for controls and diagnosis date for cases.
**10 tumours (1.7%) were of undetermined grade.
††In 449 (46.5%) cases tumour was classified as being on right side of head and in 387 (40.1%) on left side, 49 cases (5.1%) were excluded from this analysis because tumour was central, 81 cases (8.4%) because side of tumour was unknown, six others where side of phone use was unknown were also excluded.

phones overall or with time since first use, lifetime years of use, or cumulative hours or number of calls.

In Sweden Hardell et al reported raised risks for mobile phone use ipsilateral to the side of development of high grade astrocytomas (the principal subtype of glioma)[8] and for rural use in different analyses of the same study.[9] Several other studies, however, could not confirm these results and the methods were criticised.[3 20 21] Our laterality analyses both showed a significantly raised risk for ipsilateral phone use. Using the methods of Lonn et al,[17] however, we found a significantly reduced risk for contralateral use. These "complementary risks" above and below unity, which we observed for all measures of mobile phone use, can probably be explained by recall bias.[21] The patients with glioma, who were aware of the location of their tumour, may have considered that mobile phone use was a cause of its development, resulting in systematically over-reporting of phone use on the side of the head where their cancer occurred. Generally, individuals are likely to overestimate their actual use of mobile phones,[22] and this may have exaggerated the effect of differential reporting for laterality. To investigate this issue further, we made case-control comparisons by handedness as people tend to use the phone on their handed side and because handedness is a variable reported at interview and not likely to be subject to recall bias. The clear pattern of significant odds ratios above and below unity for ipsilateral and contralateral mobile phone use, respectively, was not seen for handedness in equivalent analyses.

Table 3 Odds ratios and 95% confidence intervals for risk of glioma in relation to use of analogue phones

Factor and level of exposure	Cases	Controls	Odds ratio (95% CI)
Frequency of use*:			
Never/non-regular	456 (47.2)	818 (47.7)	1.0
Digital only	378 (39.1)	685 (39.9)	0.96 (0.79 to 1.16)
Regular analogue	128 (13.3)	212 (12.4)	0.87 (0.66 to 1.15)
Not known	4 (0.4)	1 (0.1)	—
Years since first use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.0
Digital only	378 (39.1)	685 (39.9)	0.96 (0.79 to 1.16)
1.5-4†	15 (1.6)	33 (1.9)	0.59 (0.30 to 1.15)
5-9	56 (5.8)	84 (4.9)	0.98 (0.66 to 1.45)
≥10	56 (5.8)	95 (5.5)	0.87 (0.59 to 1.27)
Not known	5 (0.5)	1 (0.1)	—
Lifetime years of use:			
Never/non-regular	456 (47.2)	818 (47.7)	1.0
Digital only	378 (39.1)	685 (39.9)	0.96 (0.79 to 1.16)
0.5-4	90 (9.3)	159 (9.3)	0.82 (0.60 to 1.11)
5-9	27 (2.8)	42 (2.4)	0.97 (0.57 to 1.66)
≥10	10 (1.0)	11 (0.6)	1.20 (0.48 to 3.04)
Not known	5 (0.5)	1 (0.1)	—
Cumulative hours of use ≥10 years ago‡:			
Never/non-regular	456 (47.2)	818 (47.7)	1.0
Digital only	378 (39.1)	685 (39.9)	0.95 (0.79 to 1.16)
<10 years	69 (7.1)	115 (6.7)	0.86 (0.61 to 1.22)
≥10 years, ≤126 hours	23 (2.4)	47 (2.7)	0.70 (0.41 to 1.21)
≥10 years, >126 hours	31 (3.2)	47 (2.7)	0.98 (0.59 to 1.62)
Not known	9 (0.9)	4 (0.2)	—

*Of 4055 phones reported by participants, 586 (14.5%) were analogue, 3183 (78.5%) were digital, and 286 (7.1%) could not be classified.
†Lower limit 1.5 years ago because regular phone use defined as phone use of at least six months' duration at least one year before reference date.
‡Use ≥10 years before reference date for controls and diagnosis date for cases.

Potential bias

Case-control studies are subject to certain biases and particularly participation bias.[23] We interviewed 51% of those patients with glioma who were eligible, mainly because rapid death prevented us from approaching all of them. As early death is most likely in patients with high grade tumours, it is not surprising that participation rates were higher in those with low grade tumours. A bias in these results would occur only if mobile phone use was related to severity of tumour, which was not supported by our analysis, where odds ratios for mobile phone use showed no increased risk for high or low grade tumours.

There is also potential for the introduction of participation bias into the control group. All controls were selected to represent the general population by using the sampling frame of general practitioners' lists. Although methods varied between the south east and northern centres, the analysis strategy of frequency matching permitted a combined approach. The overall response rate for controls was relatively low (45%) compared with previously published studies from the Nordic countries[6 7] on mobile phone use and risk of glioma. Recruitment of controls was a complicated procedure, and we tried to optimise participation rates. Prevailing legislation on consent from patients made the process a resource intensive exercise for general practitioners and in some instances the study could not follow-up patients directly, instead relying on general practitioners to undertake this process. The principal reason for non-participation of controls was that they were "uncontactable," and constraints imposed by ethical approval bodies prevented more than one follow-up attempt. It is likely, therefore, that some of the apparent non-responders were in fact individuals who were never contacted and therefore had no opportunity to respond. Our interviewed controls were more affluent than their non-interviewed counterparts and the interviewed patients with glioma. Though we adjusted for deprivation in all the analyses, this cannot completely remove its potential influence.

There is generally a lack of convincing and consistent evidence of any effect of exposure to radiofrequency field on risk of cancer.[24 25] Overall our findings are consistent with this and with most studies on mobile phone use. The positive association found between risk of glioma and ipsilateral mobile phone use was accompanied by a negative association for the opposite side of use to the tumour. Although it is possible the ipsilateral association represents a real effect, this finding is probably explained by recall bias, with patients with glioma systematically over-reporting use on the same side as their tumour and consequently under-reporting use on the opposite side. This study suggests that there are no substantially raised risks of glioma in the 10 years after first mobile phone use. Only future studies will be able to address longer latency periods for the development of glioma.

We thank all the individuals who were interviewed for this project; all the study interviewers, administrators, and computer programmers who collected and processed the data; and Elisabeth Cardis, the coordinator of the Interphone study, and her colleagues for support and provision of data. The Northern UK study acknowledges the support of the membership of the study steering group chaired by David Coggon and the following neuropathologists, neuroradiologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, specialist nurses, and administrators based in hospitals located in Scotland (P Barlow, I Bone, J Brown, J Crowther, R

What is already known on this topic

Gliomas are a specific type of brain tumour for which the causes are generally unknown, but concern has been expressed over a possible link with using a mobile phone

What this study adds

This large case-control study found no increased risk of developing a glioma associated with mobile phone use either in the short or medium term

Dolan, L Dunn, M O Fitzpatrick, M Fraser, R Grant, A Gregor, J Ironside, R Johnstone, K W Lyndsay, S Macnamara, J Mair, R Mills, L Myles, B O'Reilly, V Papanastassiou, R Rampling, M Russell, D Sim, P Statham, J Steers, W A Taylor, G Teasdale, I Whittle), West Midlands (J M Anderson, P Barber, C R Barraclough, P Bennett, H G Boddie, A Brind, P Carey, M Choksey, M Christie, R N Corston, G S Cruickshank, A Detta, P Dias, S J Ellis, G Flint, D A Francis, A H Grubneac, S P Harland, C Hawkins, T Heafield, R C Hughes, D G Jamieson, A Logan, C H A Meyer, R Mitchell, K Morrison, P Newman, D Nicholl, S Nightingale, H S Pall, J R Ponsford, A Shehu, J Singh, J A Spillane, P Stanworth, B Summers, A R Walsh, J Wasserberg, A C Williams, J Winer, S Zygmunt), Trent (R J Abbott, S Adams, R D Ashpole, R D E Battersby, L Blumhardt, P Byrne, M Cartmill, S C Coley, P Critchley, B B Faraj, A Gibson, P Griffiths, R Grunwald, T J Hodgson, D T Hope, S Howell, D Jefferson, D Jelinek, N Jordan, A Kemeny, M C Lawden, J Lowe, N Messios, Kirsty Pardoe, S Price, I F Pye, M Radatz, I Robertson, K Robson, C Romanowski, G Sawle, B Sharrock, P Shaw, C Smith, W Temperley, G Venables, B White, A M Whiteley, AJ Wills), and West Yorkshire (A S N Al-Din, D Ash, J Bamford, M Bond, G Bonsor, L Bridges, B Carey, A Chakrabarty, P Chumas, D Dafalla, H Ford, G E Gerrard, P J Goulding, J Howe, S Jamieson, M H Johnson, L A Louizou, P Marks, M Nelson, S Omer, N Phillips, S Ross, I Rothwell, H Spokes, J Straiton, G Towns, A Tyagi, P Vanhille, M Busby).The Southeast England study thanks D Hogben for study administration and their research nurses, A Butlin, J Owens, A Hart, R Knight, C Parsley, M Pelerin, K Sampson and M Swanwick, for data collection. They thank H Møller, B Plewa, and S Richards from the Thames Cancer Registry and the following neuropathologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, administrators, and secretaries for the help they provided: D G Hardy, P J Kilpatrick, R Macfarlane (Addenbrooke's Hospital); M Cronin, T Foster, S Furey, M G Glaser, F Jones, N D Mendoza, E S Newlands, K S O'Neill, D Peterson, F Taylor, J van Dellon (Charing Cross Hospital); J J Bending (Eastbourne District Hospital); P R Bullock, C Chandler, B Chitnavis, L Doey, R W Gullan, C E Polkey, R Selway, M M Sharr, L Smith, A J Strong, N Thomas (King's College Hospital); G M Sadler (Maidstone Hospital); S Short (Mount Vernon Hospital); S Brandner, A D Cheesman, J P Grieve, W J Harkness, R Kapoor, N D Kitchen, T Pearce, M P Powell, J Rees, F Scaravilli, D T Thomas, L D Watkins (National Hospital for Neurology and Neurosurgery); A R Aspoas, S Bavetta, J C Benjamin, K M David, J R Pollock, E Sims (Oldchurch Hospital); J Armstrong, J Akinwunmi, G Critchley, L Gunasekera, C Hardwidge, J S Norris, P E Rose, P H Walter, P J Ward, M Wilkins (Princess Royal Hospital); T Z Aziz, D Kerr, P J Teddy (Radcliffe Infirmary); M Allen, T Dale, R Bradford, A P Dhillon, N L Dorward, D Farraday-Browne, D J McLaughlin, R S Maurice-Williams, K Pigott, B Reynolds, C Shah, C Shieff, E M Wilson (Royal Free Hospital); F Afshar, H E Ellamushi, P M Richardson, H I Sabin, J Wadley (Royal London Hospital); M Brada, F H Saran, D Traish (Royal Marsden Hospital); S Whitaker (Royal Surrey County Hospital); P N Plowman (St Bartholomew's Hospital); Carole Bramwell, A Bell, F Johnston, H Marsh, A Martin, P S Minhas, A Moore, S Stapleton, S Wilson (St George's Hospital); R P Beaney (St Thomas' Hospital).

Contributors: PAMcK, MJS, KRM, MJAvT, and AJS were responsible for the design and implementation of the study. SJH and MJS conducted the statistical analysis. PAMcK and SJH wrote the first draft of the paper. All coauthors provided comments on the draft. PAMcK is the guarantor.

Funding: The south east and northern UK studies received funding from the Mobile Telecommunications, Health and Research (MTHR) programme and as part of the Interphone study from the EU, the Mobile Manufacturers Forum, and the GSM Association through the scientifically independent Union Internationale Contre le Cancer (UICC). In addition the northern UK study received funding from the Health and Safety Executive, the Department of Health, the UK network operators (O_2, Orange, T-Mobile, Vodafone, 3), and the Scottish Executive.

Competing interest: The University of Leeds has received some financial support on behalf of the four centres of the UK northern study from the UK network operators (O_2, Orange, T-Mobile, Vodafone, 3) under legal signed contractual agreements which ensure complete independence for the scientific investigators. While employed at the University of Birmingham MJAvT received funding from O_2, Orange, T-Mobile, and Vodafone to carry out a feasibility study of health effects from radiofrequency exposure among employees of broadcasting and telecommunication industries.

Ethical approval: Multicentre research ethics committees for the south east and Scotland and all relevant local research ethics committees.

1 Cancer Research UK. www.cancerresearchuk.org/ (accessed 23 May 2005).
2 Sienkiewicz ZJ, Kowalczuk CI. *A summary of recent reports on mobile phones and health (2000-2004).* Didcot, Oxon: National Radiological Protection Board, 2005. (NRPB-W65.)
3 Advisory Group on Non-ionising Radiation (AGNIR). Health effects from radiofrequency electromagnetic fields. Report of an advisory group on non-ionising radiation. *Document of the NRPB* 2003;14:1-177. www.hpa.org.uk/radiation/publications/documents_of_nrpb/abstracts/absd14-2.htm (accessed 1 June 2005).
4 Inskip PD, Tarone RE, Hatch EE, Wilcosky TC, Shapiro WR, Selker RG, et al. Cellular-telephone use and brain tumors. *N Engl J Med* 2001;344:79-86.
5 Muscat JE, Malkin MG, Thompson S, Shore RE, Stellman SD, McRee D, et al. Handheld cellular telephone use and risk of brain cancer. *JAMA* 2000;284:3001-7.
6 Lonn S, Ahlbom A, Hall P, Feychting M, the Swedish Interphone Study Group. Long-term mobile phone use and brain tumor risk. *Am J Epidemiol* 2005;161:526-35.
7 Christensen HC, Schuz J, Kosteljanetz M, Poulsen HS, Boice JD, McLaughlin JK, et al. Cellular telephones and risk for brain tumours. *Neurology* 2005;64:1189-95.
8 Hardell L, Hansson Mild K, Carlberg M. Further aspects on cellular and cordless telephones and brain tumours. *Int J Oncol* 2003;22:399-407.
9 Hardell L, Carlberg M, Hansson Mild K. Use of cellular telephones and brain tumour risk in urban and rural areas. *Occup Env Med* 2005;62:390-4.
10 Auvinen A, Hietanen M, Luukkonen R, Kosela R-S. Brain tumors and salivary gland cancers among cellular telephone users. *Epidemiology* 2002;13:356-9.
11 Cardis E, Kilkenny M. International case-control study of adult brain, head and neck tumours: results of the feasibility study. *Radiat Prot Dosimetry* 1999;83:179-83.
12 World Health Organization. *International classification of diseases for oncology.* 3rd ed. Geneva: WHO, 2000.
13 Kleihues P, Cavenee WK. *Pathology and genetics of tumours of the central nervous system.* Lyon: International Agency for Research on Cancer, 1997.
14 Office of Population Censuses and Surveys. *General practitioner morbidity statistics.* London: OPCS, 1992.
15 Lonn S, Forssen U, Vecchia P, Ahlbom A, Feychting M. Output power levels from mobile phones in different geographical areas; implications for exposure assessment. *Occup Environ Med* 2004;61:769-72.
16 Townsend P, Phillimore P, Beattie A. *Health and deprivation: inequality and the north.* New York: Croom Helm, 1988.
17 Lonn S, Ahlbom A, Hall P, Feychting M. Mobile phone use and the risk of acoustic neuroma. *Epidemiology* 2004;15:653-9.
18 Johansen C, Boice J Jr, McLaughlin J, Olsen J. Cellular telephones and cancer—a nationwide cohort study in Denmark. *J Natl Cancer Inst* 2001;93:203-7.
19 Dimbylow P, Mann S. Characterisation of energy deposition in the head from cellular phones. *Radiat Prot Dosimetry* 1999;83:139-41.
20 Boice JD, McLaughlin JK. *Epidemiologic studies of cellular telephones and cancer risk—a review. SSI Report.* Stockholm: Swedish Radiation Protection Authority, 2002.
21 Rothman KJ. Epidemiological evidence on health risks of cellular phones. *Lancet* 2000;356:1837-40.
22 Parslow RC, Hepworth SJ, McKinney PA. Recall of past use of mobile phone handsets. *Radiat Prot Dosimetry* 2003;106:233-40.
23 Law GR, Smith AG, Roman E. The importance of full participation: lessons from a national case-control study. *Br J Cancer* 2002;86:350-5.
24 Habash RWY, Brodsky LM, Leiss W, Krewski D, Repacholi M. Health risks of electromagnetic fields. Part II: Evaluation and assessment of radio frequency radiation. *Crit Rev Biomed Eng* 2003;31:197-254.
25 Ahlbom A, Green A, Kheifets L, Savitz D, Swerdlow A. Epidemiology of health effects of radiofrequency exposure. *Environ Health Perspect* 2004;112:1741-54.

(Accepted 14 November 2005)

doi 10.1136/bmj.38720.687975.55

Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health, and Therapeutics (LIGHT), Leeds LS2 9LN
Sarah J Hepworth *medical statistician*
Patricia A McKinney *professor of paediatric epidemiology*

Institute of Cancer Research, Section of Epidemiology, Sutton, Surrey SM2 5NG
Minouk J Schoemaker *medical statistician*
Anthony J Swerdlow *professor of epidemiology*

Division of Epidemiology and Public Health, School of Community Health Sciences, Queen's Medical Centre, Nottingham NG7 2UH
Kenneth R Muir *professor of epidemiology*

Centre for Occupational and Environmental Health, Division of Epidemiology and Health Sciences, University of Manchester, Manchester M13 9PL
Martie J A van Tongeren *senior lecturer in occupational and environmental health*

Correspondence to: P A McKinney p.a.mckinney@leeds.ac.uk

Cite this article as: BMJ, doi:10.1136/bmj.38765.519850.55 (published 6 March 2006)

Research

Are some people sensitive to mobile phone signals? Within participants double blind randomised provocation study

G James Rubin, Gareth Hahn, Brian S Everitt, Anthony J Cleare, Simon Wessely

Abstract

Objective To test whether people who report being sensitive to mobile phone signals have more symptoms when exposed to a pulsing mobile signal than when exposed to a sham signal or a non-pulsing signal.
Design Double blind, randomised, within participants provocation study.
Setting Dedicated suite of offices at King's College London, between September 2003 and June 2005.
Participants 60 "sensitive" people who reported often getting headache-like symptoms within 20 minutes of using a global system for mobile communication (GSM) mobile phone and 60 "control" participants who did not report any such symptoms.
Intervention Participants were exposed to three conditions: a 900 MHz GSM mobile phone signal, a non-pulsing carrier wave signal, and a sham condition with no signal present. Each exposure lasted for 50 minutes.
Main outcome measures The principal outcome measure was headache severity assessed with a 0-100 visual analogue scale. Other outcomes included six other subjective symptoms and participants' ability to judge whether a signal was present.
Results Headache severity increased during exposure and decreased immediately afterwards. However, no strong evidence was found of any difference between the conditions in terms of symptom severity. Nor did evidence of any differential effect of condition between the two groups exist. The proportion of sensitive participants who believed a signal was present during GSM exposure (60%) was similar to the proportion who believed one was present during sham exposure (63%).
Conclusions No evidence was found to indicate that people with self reported sensitivity to mobile phone signals are able to detect such signals or that they react to them with increased symptom severity. As sham exposure was sufficient to trigger severe symptoms in some participants, psychological factors may have an important role in causing this condition.
Trial registration ISRCTN81432775.

Introduction

The recent uptake of mobile phones has been accompanied by some concern about possible health risks.[1] In the general population, the health effects most often attributed to mobile phone use are non-specific symptoms. Excluding sensations of mild warmth, the most commonly reported symptoms are headache, burning, dizziness, fatigue, and tingling.[2] Mechanisms to explain these phenomena remain speculative, and although the pulsing nature of "global system for mobile communication" (GSM) signals has been suggested to be partly to blame,[3] experiments that have exposed healthy adults to GSM signals under blind conditions have not found any significant effects on the reporting of symptoms.[4]

Whether a subgroup of people who are more sensitive to GSM exists remains unclear. Of particular interest are people who report symptoms almost every time they use a mobile phone.[5] This phenomenon falls within the broader category of "electromagnetic sensitivity," a medically unexplained condition in which non-specific symptoms are reported after perceived exposure to any of a wide range of electrical devices, including mobile phones, visual display units, and power lines. The prevalence of self reported electromagnetic sensitivity in the United Kingdom is unknown, but community studies in Sweden and California put the figure at between 1.5% and 3%.[6 7] Provocation studies that have exposed people who report electromagnetic sensitivity to electromagnetic fields under blind conditions have so far failed to provide any good evidence linking the presence of electromagnetic fields to severity of symptoms.[8] Several authors have therefore suggested that psychological mechanisms may be more relevant in causing the condition.[9]

We tested whether people with self reported sensitivity to GSM would experience greater headache severity after double blind exposure to a GSM signal than after exposure to a sham signal. Secondary outcomes included other symptoms and ability to discriminate GSM from sham signals. We also tested whether a pulsing signal resulted in greater reporting of symptoms than a non-pulsing signal.

Methods

Study design

In this within participants study, we exposed people who reported adverse reactions to mobile phone signals (sensitive group) or who did not report any such effects (control group) to three conditions: a signal mimicking that produced by a 900 MHz GSM mobile phone, an unpulsed continuous wave signal, and a sham exposure with no signal present. Our Clinical Trials Unit determined the order in which these conditions occurred for each participant on enrolment, by using a computerised random numbers generator and counter-balancing within blocks of six consecutive participants.

Exposures were double blind—that is, neither participants nor researchers were told which type of exposure was present in which testing session. The controls for our exposure equipment allowed for 256 possible settings, of which 15 had been randomly allocated to each condition. Only the Clinical Trials Unit knew which settings related to which exposure. For the first nine control participants and six sensitive participants (11.5% of all participants), Clinical Trials Unit staff told researchers which

setting to use on the morning of each exposure. Given the theoretical possibility that the meaning of a setting might eventually be inferred by observing several participants' reactions to it, for the remaining sessions Clinical Trials Unit staff entered the codes and then obscured them from the researchers with opaque tape.

Participants

To be eligible for the sensitive group, participants had to report often experiencing headache-like symptoms within 20 minutes of using a 900 MHz GSM mobile phone. Participants who did not attribute any symptoms to mobile phone signals were eligible for the control group. We excluded people who were aged under 18 or over 75, were pregnant, had a psychotic illness, were currently using antidepressants, or reported severe symptoms at baseline while in our testing room. We recruited participants through mailshots organised by an electromagnetic sensitivity support group, advertising by interested clinicians and by our funding body, posters in general practitioners' surgeries, adverts and articles in the press and specialist health publications, email circulars, and word of mouth.

Exposures

We generated exposures by using the standard GSM handset system used within the UK Mobile Telecommunications and Health Research programme.[10] The antenna for this headband mounted system was positioned slightly above and behind the left ear and within a few millimetres of the participant's scalp. Both GSM and continuous wave conditions produced a target specific absorption rate adjacent to the antenna of 1.4 W/kg, with an uncertainty of ±30%. For the sham exposure, a continuous wave signal was generated to ensure that the system heated up to the same degree as the active exposures but was diverted to an internal load instead of being transmitted through the antenna; only minimal leakage of this signal occurred (specific absorption rate <0.002 W/kg).

Questionnaires

We assessed severity of symptoms during exposure by using 100 mm visual analogue scales,[11] anchored with the phrases "no sensation" and "worst possible sensation." These scales measured headaches; nausea; fatigue; dizziness; skin itching, tingling, or stinging; sensations of warmth or burning on skin; and eye pain or dryness.

We collected other data at baseline, consisting of demographics and current or previous mobile phone usage. We also asked participants to record the frequency with which they experienced 11 common symptoms after a mobile phone call (never, 25% of calls, 50% of calls, 75% of calls, every call). We asked participants in the sensitive group about duration of illness and symptoms, how near a mobile phone needed to be before they could detect it, whether they considered themselves to have "electrosensitivity or sensitivity to electromagnetic fields," whether they had sought treatment, and whether their sensitivity impaired their daily functioning.[12]

Procedure

We sent written information to people who contacted us and screened them for eligibility. We invited those who provided verbal consent to attend our unit for three mornings. We instructed participants not to take recreational drugs for one week before attending; not to drink alcohol for 24 hours beforehand; and not to drink more than one cup of tea or coffee, take painkillers, or undertake strenuous physical activity or anything psychologically stressful on the morning of each visit.

Sessions began with a 30 minute adjustment period. During this time in session one, participants provided informed written consent and completed the various demographic questionnaires. At the end of these adjustment periods, we asked participants to complete baseline visual analogue scale measures. The exposure equipment was then attached and switched on for 50 minutes. Participants completed further visual analogue scale measures after 5, 15, 30, and 50 minutes. If a participant requested that an exposure be terminated early, visual analogue scales were administered immediately. All participants completed a final set of visual analogue scales 30 minutes after the end of each exposure. At this point we asked them to state whether they believed a signal had been present and their confidence about this (100 mm visual analogue scales from "complete guess" to "100% certain"). At least 24 hours after each session we contacted participants and asked them whether they had experienced any visual analogue scale symptoms in the 24 hours since exposure. We ascertained a score of 0 (no sensation) to 10 (worst possible sensation) for any symptoms that were reported, and we categorised participants scoring 5 or more as having experienced a "definite" symptom.

All testing took place between September 2003 and June 2005 in two rooms within King's College London. The rooms, which were lit by two table lamps, were not shielded against outside electromagnetic fields.

Sample size calculation

We based our sample size calculation on our ability to detect a change in headache severity within the sensitive group after 50 minutes of GSM exposure, using a two way analysis of variance with one between participants factor (sensitive *v* control) and one within participants factor (GSM *v* continuous wave *v* sham). On the basis of previous studies in healthy and electrosensitive participants,[4 13] this analysis assumed that control participants would report a mean headache severity of 10 units in all three experimental conditions whereas sensitive participants would report a mean severity of 11.7 in the sham and continuous wave conditions, with standard deviations of 26.8. In the absence of any pre-existing data, we assumed correlations of $r=0.5$ between conditions and that any effect of GSM in the sensitive group would be moderate—that is, an effect size of 0.5. Our calculation showed that to detect this effect as significant at the 5% level and with 80% power we would need 60 participants in each group. In practice, although these assumptions turned out to be reasonable, the nature of our data required us to adopt a different analytical strategy from that originally planned. As such, this calculation should be taken as indicative only.

Analyses

To analyse symptom severity over time, we used generalised estimating equations.[14] This approach was needed to accommodate the extremely positively skewed distribution of each response variable and to allow the inclusion of a suitable correlation structure for the repeated measures of each response. These models also allowed us to take into account differing lengths of exposure for participants who requested that an exposure be terminated early. The specific generalised estimating equations model fitted to each response used log(symptom severity+1) as the dependent variable, a gamma error distribution, and an exchangeable correlation structure. We used robust standard errors to judge the "significance" or otherwise of the explanatory variables included in the fitted models.[14]

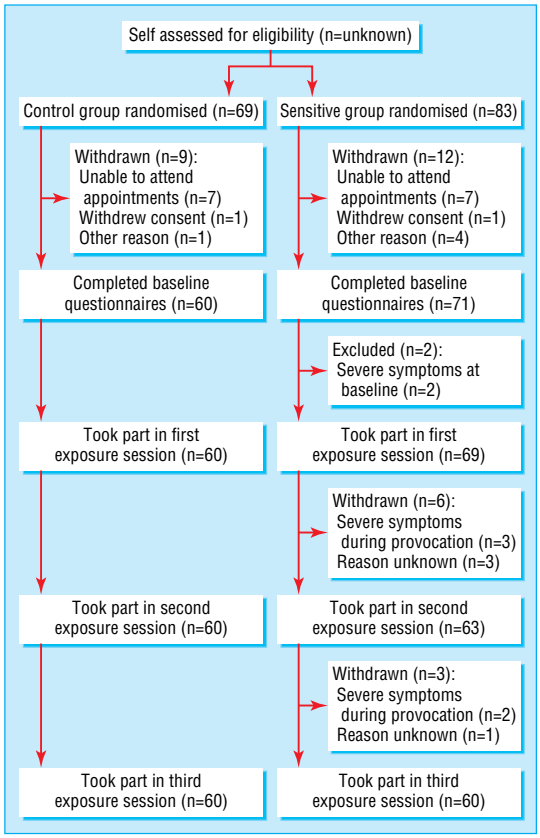

Fig 1 Study flow diagram

Results

We were contacted by 83 potential sensitive participants and 69 potential controls who met the inclusion criteria and provided verbal consent. Of these, 71 sensitive participants and 60 controls attended for their first testing session, and 60 in each group attended all three testing sessions and were included in our main generalised estimating equations analyses (fig 1). Table 1 shows demographic data for those participants who attended at least one session; the only substantive difference between the groups was a significantly higher proportion of sensitive participants from a professional or managerial background ($\chi^2=5.6$, $P=0.02$). Restricting the demographic comparisons to participants who completed all three testing sessions did not alter these results.

For sensitive participants, the mean reported delay between beginning a call and onset of symptoms in everyday life was 6.5 (SD 6.5) minutes. For 48 people, symptoms usually resolved within two hours. All but one had been sensitive for at least a year (median 4 (interquartile range 2-5) years). Eighteen people reported that their sensitivity to mobile phones caused "definite" impairment or worse in at least one aspect of daily functioning, and 15 people reported having sought treatment for their condition. Thirteen people reported being sensitive to mobile phones at distances of one metre or more, and the same number reported having "electrosensitivity." Sensitive participants reported headache-like symptoms in a mean of 70.4% of calls. The next most common symptoms were skin warmth or burning (43.8% of calls), difficulty concentrating (30.0%), and dizziness (20.8%). Very few control participants reported any symptoms in relation to mobile phone signals; the highest mean frequency was for skin warmth or burning (2.9%).

Table 1 Demographics of participants

Variable	Control group (n=60)	Sensitive group (n=71)	P value for differences between groups
Mean (SD) age (years)	33.5 (10.2)	37.1 (13.2)	0.09
Sex (male:female)	27:33	31:40	0.88
Ethnicity (white:other)	45:15	56:15	0.60
Marital status (single:married/ cohabiting:divorced/separated)	39:19:2	38:30:3	0.41
Employment status (in work:unemployed:housewife/ husband:student)	30:10:2:18	42:9:3:17	0.71
Socioeconomic status (professional, managerial, or intermediate:semiroutine, routine, or student)	31:29	51:20	0.02
Educational level (secondary education or lower:higher education)	18:42	26:45	0.42
Weekly frequency of mobile phone use (<4 times:4-12 times:13+ times)*	8:25:27	17:22:32	0.23
Typical length of call (<5 minutes:5-15 minutes:16+ minutes)*	32:22:6	44:18:9	0.37

*Former mobile users (n=10) based their answers on the last time they regularly used one.

Table 2 shows the results of fitting generalised estimating equation models to each response variable. The group×time interaction term was not needed in any model, so it does not appear in this table. Fitted models for all response variables showed highly significant effects for time (both linear and quadratic effects) and for baseline severity. We found no convincing evidence of an effect of condition or a condition×group effect for any of the symptoms. For headache, burning sensations, skin sensations, and eye pain we found evidence of a main group effect—sensitive participants reported greater severity. In terms of the original visual analogue scale units, this group effect for headache severity equated to an increase of 1.0 (95% confidence interval 0.4 to 2.0) unit. Figure 2 shows the median headache severity by group for each exposure condition, and figure 3 illustrates the main effect of group on headache severity collapsed across conditions.

We also analysed the number of severe reactions seen in each condition, with a severe reaction defined as a participant requesting that an exposure be terminated early or withdrawing from the study entirely after an exposure. Twenty six such reactions occurred in the sensitive group (9 withdrawals; 17 early terminations), and none occurred in the control group. These reactions were equally distributed between GSM ($n=7$), continuous wave ($n=10$), and sham ($n=9$) conditions ($\chi^2=0.54$, $P=0.76$). Excluding data relating to the four participants whose reasons for withdrawal were not explicitly stated to us (see fig 1) did not affect these results (GSM 5, continuous wave 9, sham 8; $\chi^2=1.2$, $P=0.55$).

We had next day follow-up results for all three sessions for 41 control participants and 49 sensitive participants. Cochran's Q tests identified no significant differences in the number reporting at least one definite symptom after GSM, continuous wave, or sham exposures in either the control group (GSM 0/41, continuous wave 2/41, sham 4/41; $Q=4.0$, $P=0.14$) or the sensitive group (GSM 5/49, continuous wave 8/49, sham 4/49; $Q=2.0$, $P=0.37$).

Table 3 shows participants' assessments of whether a signal was present during provocation. The proportion who believed a signal was present during exposure to GSM (60% of sensitive participants, 58% of controls) was slightly less than for the sham

Table 2 Estimated regression coefficients (robust standard error) derived from generalised estimating equation models used to assess effects of group, exposure, duration of exposure, and baseline score on symptom severity

Symptom	Baseline severity	Duration (linear function)	Duration (quadratic function)	Sensitive *v* control	Sham *v* GSM	CW *v* GSM	Group x (sham *v* GSM)	Group x (CW *v* GSM)
Headache	0.04 (0.008)	0.04 (0.004)	−0.0004 (0.0004)	0.7 (0.2)	0.07 (0.1)	−0.02 (0.1)	−0.08 (0.2)	0.2 (0.2)
Nausea	0.02 (0.05)	0.006 (0.001)	−0.0002 (0.00004)	0.2 (0.3)	0.06 (0.1)	−0.2 (0.1)	0.1 (0.4)	0.3 (0.3)
Fatigue	0.04 (0.005)	0.01 (0.002)	−0.0003 (0.00005)	0.2 (0.2)	−0.08 (0.1)	−0.2 (0.1)	−0.09 (0.2)	0.2 (0.2)
Dizziness	0.05 (0.02)	0.007 (0.001)	−0.0003 (0.00005)	0.3 (0.2)	−0.2 (0.1)	−0.09 (0.1)	0.2 (0.3)	−0.01 (0.3)
Skin	0.05 (0.01)	0.004 (0.001)	−0.0003 (0.00005)	0.5 (0.2)	−0.09 (0.1)	−0.1 (0.1)	0.1 (0.2)	0.3 (0.2)
Burning	0.03 (0.00005)	0.007 (0.001)	−0.0007 (0.0004)	0.4 (0.2)	−0.05 (0.1)	−0.09 (0.09)	0.2 (0.2)	0.4 (0.2)
Eye pain	0.05 (0.008)	0.007 (0.001)	−0.0003 (0.00004)	0.6 (0.2)	−0.04 (0.1)	0.2 (0.1)	−0.3 (0.2)	−0.08 (0.2)

CW=continuous wave; GSM=global system for mobile communication.
In each model, the dependent variable used was log(symptom severity +1).

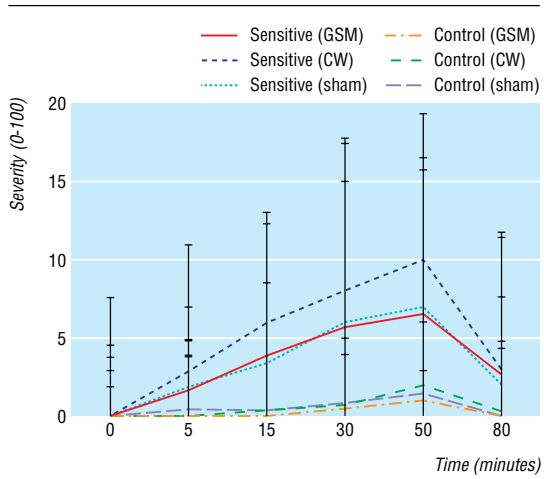

Fig 2 Median headache severity (error bars show interquartile range) during provocation with global system for mobile communication (GSM), continuous wave (CW), and sham exposures for sensitive and control participants. For clarity, graph does not include data relating to exposures that were terminated early, although these data were included in analyses

exposure (63% of sensitive participants, 68% of controls). Self reported confidence for these judgments did not differ greatly (table 3).

Discussion

We found no evidence to indicate that self reported sensitivity to 900 MHz GSM mobile phone signals has a biological basis. Nor did we find any evidence to suggest that the pulsing nature of GSM contributes to these symptoms. These findings agree with the large majority of previous blind or double blind provocation studies for electromagnetic sensitivity, which have found no differences in the severity of symptoms elicited by active or sham exposure to electromagnetic fields.[8]

Did some inadequacy exist in our methods that might account for these "negative" findings? If it did, we are unaware of it. The exposure represented a relatively "worst case scenario" mobile phone call, using a high specific absorption rate and lasting almost eight times longer than the mean call length usually needed to trigger symptoms in our sensitive sample. Interference from participants' reactions to extraneous electromagnetic fields is also unlikely: after 30 minutes adjusting to our offices, only two

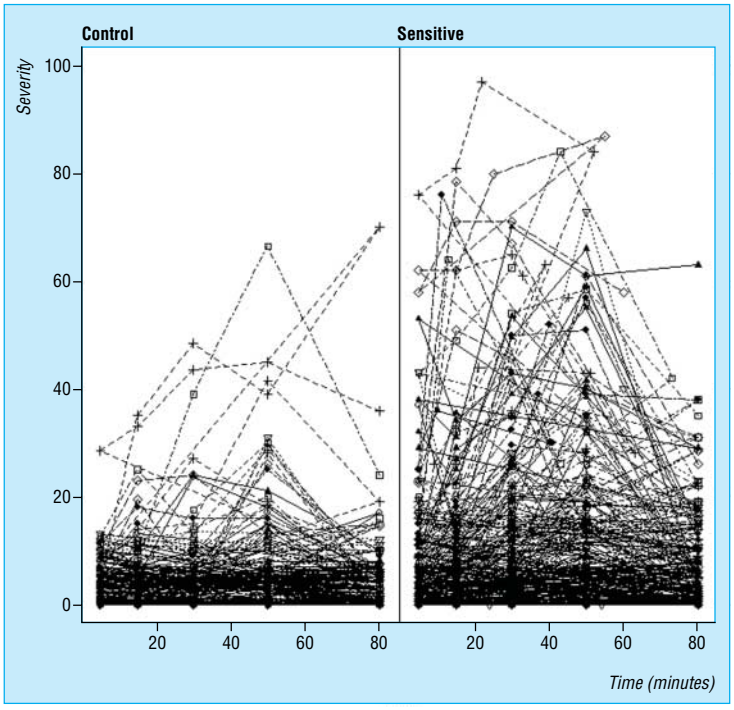

Fig 3 Headache severity over time for each participant, illustrating main effect of group on severity. Data for this figure have been collapsed across all three exposure conditions

Table 3 Number of participants who believed a signal was present for each experimental condition and mean (SD) confidence (0-100) reported by participants for these "signal present" assessments

Exposure	Controls		Sensitive participants			
			Completed all three exposures		Completed at least one exposure	
	No	Confidence	No	Confidence	No	Confidence
GSM	35/60	36.8 (28.5)	36/60	58.6 (30.8)	41/65	61.2 (31.0)
CW	42/60	39.7 (33.0)	41/60	57.7 (27.8)	45/64	57.8 (28.9)
Sham	41/60	43.9 (31.9)	38/60	64.4 (31.7)	39/63	64.0 (31.3)

CW=continuous wave; GSM=global system for mobile communication.

participants reported baseline symptoms that might have masked any effects of exposure, and both were excluded. Finally, as we were able to detect changes in symptom severity over time as highly significant, the sensitivity of our visual analogue scales and our statistical techniques do not seem to have had any shortcomings.

That symptom severity did increase during exposure is interesting. These symptoms were not trivial. Indeed, for some they were so severe that exposures had to be stopped early or the participants withdrew from the study. The confidence that sensitive participants had in their ability to discriminate active from sham signals also suggests that they experienced reactions similar to those encountered in real life, a finding also reported in previous provocation studies.[8] That apparently realistic symptoms can be induced in provocation experiments, despite no differences being observed between active and sham conditions, suggests that the acute symptoms reported by sensitive people in everyday life may be the result of a nocebo phenomenon. Such phenomena have previously been observed in relation to a wide range of stimuli,[15] including headaches induced by providing misleading information about the presence of electrical fields.[16] The mechanisms governing nocebo effects need further study but seem to include conscious expectation of symptoms and the presence of negative affect,[17 18] factors that are likely to be present whenever people who perceive themselves to be sensitive to mobile phones have to make use of the technology.

In terms of their clinical implications, these results do not suggest that attempting to reduce exposure to mobile phone signals will be a useful strategy for patients who report sensitivity to them. Although such interventions might be actively sought by patients and may even produce a short term reduction in symptoms mediated by a placebo effect,[19] in the longer term a danger exists that they will reinforce a patient's view of himself or herself as being sensitive to electromagnetic fields and put him or her at risk of developing symptoms associated with other electrical stimuli. Instead, it may be better to encourage such patients to test alternative non-electromagnetic field related explanations for their symptoms by using principles derived from cognitive behavioural therapy.[9]

We thank everybody who participated in this study, especially those in the sensitive group. We also thank Phil Chadwick from MCL-UK for supplying and calibrating the exposure equipment, and the staff from the Mental Health and Neurology Clinical Trials Unit at the Institute of Psychiatry for doing the randomisation and double blinding of the study.

Contributors: GJR had the original idea for the study and developed the study design with AJC, GH, and SW. GH and GJR did the testing. BSE analysed the symptom severity data; GJR did all other analyses. GJR wrote the first draft of the paper, and all authors contributed to further drafts. SW is the guarantor.

Funding: This study was funded by the Programme Management Committee (PMC) of the Mobile Telecommunications and Health Research (MTHR) programme (www.mthr.org.uk), an independent body set up to provide funding for research into the possible health effects of mobile telecommunications. The MTHR is itself jointly funded by the UK Department of Health and the mobile telecommunications industry. The PMC contributed to the study design by proposing a reduction in overlap with other ongoing studies by focusing on symptom reporting, an increase in sample size, and an alteration in inclusion criteria to allow more highly sensitive people to participate. It had no role in the collection, analysis, or interpretation of the data, writing of the report, or decision to submit the paper for publication. The views expressed in this paper are those of the authors and not necessarily those of the funders.

Competing interests: None declared.

Ethical approval: The South London and Maudsley NHS Trust Research Ethics Committee granted approval for the study.

1 National Radiological Protection Board. Mobile phones and health 2004: report by the board of the NRPB. *Documents of the NRPB* 2004;15.
2 Oftedal G, Wilen J, Sandstrom M, Mild KH. Symptoms experienced in connection with mobile phone use. *Occup Med* 2000;50:237-45.
3 Hyland GJ. Physics and biology of mobile telephony. *Lancet* 2000;356:1833-6.
4 Koivisto M, Haarala C, Krause CM, Revonsuo A, Laine M, Hamalainen H. GSM phone signal does not produce subjective symptoms. *Bioelectromagnetics* 2001;22:212-5.
5 Hocking B. Preliminary report: symptoms associated with mobile phone use. *Occup Med* 1998;48:357-60.
6 Hillert L, Berglind N, Arnetz BB, Bellander T. Prevalence of self-reported hypersensitivity to electric or magnetic fields in a population-based questionnaire survey. *Scand J Work Environ Health* 2002;28:33-41.
7 Levallois P, Neutra R, Lee G, Hristova L. Study of self-reported hypersensitivity to electromagnetic fields in California. *Environ Health Perspect* 2002;110(suppl 4):619-23.
8 Rubin GJ, Das Munshi J, Wessely S. Electromagnetic hypersensitivity: a systematic review of provocation studies. *Psychosom Med* 2005;67:224-32.
9 Rubin G, Das Munshi J, Wessely S. A systematic review of treatments for electromagnetic hypersensitivity. *Psychother Psychosom* 2006;75:12-8.
10 MCL MTHR GSM and TETRA handset exposure systems for human volunteer studies. www.mcluk.org/MTHR_exposure_systems (accessed 23 Dec 2005).
11 McDowell I, Newell C. Visual analogue pain rating scales. In: McDowell I, Newell C, eds. *Measuring health: a guide to rating scales and questionnaires*. Oxford: Oxford University Press, 1996:341-6.
12 Mundt JC, Marks IM, Shear MK, Greist JH. The work and social adjustment scale: a simple measure of impairment in functioning. *Br J Psychiatry* 2002;180:461-4.
13 Andersson B, Berg M, Arnetz BB, Melin L, Langlet I, Liden S. A cognitive-behavioral treatment of patients suffering from 'electric hypersensitivity': subjective effects and reactions in a double-blind provocation study. *J Occup Environ Med* 1996;38:752-8.

What is already known on this topic

Non-specific symptoms such as headaches, tingling sensations, and fatigue are sometimes attributed to mobile phone use

No generally accepted mechanisms exist that might explain how mobile phone signals could cause such effects

A minority of people also report being particularly sensitive to mobile phones, experiencing symptoms almost every time they use one

What this study adds

The signals produced by 900 MHz GSM mobile phones do not cause greater subjective symptoms than sham exposures in which no signal is present, even in people who report sensitivity to mobile phones

The symptoms reported by "sensitive" people may be the result of a nocebo effect and may be primarily psychological in origin

14 Everitt B. *Modern medical statistics*. London: Arnold, 2003.
15 Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;287:622-7.
16 Schweiger A, Parducci A. Nocebo: the psychologic induction of pain. *Pavlov J Biol Sci* 1981;16:140-3.
17 Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectations and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 2003;23:4315-23.
18 Petrie KJ, Moss-Morris R, Grey C, Shaw M. The relationship of negative affect and perceived sensitivity to symptom reporting following vaccination. *Br J Health Psychol* 2004;9:101-11.
19 Oftedal G, Nyvang A, Moen BE. Long-term effects on symptoms by reducing electric fields from visual display units. *Scand J Work Environ Health* 1999;25:415-21.

(Accepted 9 February 2006)

doi 10.1136/bmj.38765.519850.55

King's College London, Institute of Psychiatry, Department of Psychological Medicine, Section of General Hospital Psychiatry, Weston Education Centre (PO62), London SE5 9RJ
G James Rubin *research fellow*
Gareth Hahn *senior research nurse*
Anthony J Cleare *senior lecturer*
Simon Wessely *professor of epidemiological and liaison psychiatry*

King's College London, Institute of Psychiatry, Department of Biostatistics and Computing, London SE5 8AF
Brian S Everitt *professor emeritus of biostatistics*

Correspondence to: G J Rubin g.rubin@iop.kcl.ac.uk