Letters to the editor

'Causes of excess mortality in cerebral palsy'

SIR–*We were interested to read Strauss et al.'s paper reporting causes of excess mortality in cerebral palsy (CP) compared with the general population[1]. These potentially very important excess 'causes of death' included some cancers, and diseases of the circulatory and respiratory systems. A major strength of their study was that the dataset of individuals was very large (n=4028 deaths). Various reasons for the excess mortality were discussed, including possible causal links as well as differential health service use and treatment strategies. If substantiated, such an excess would have major implications for prevention strategies in CP and for addressing inequity in service provision. Before attaching too much credence to the results, however, considerable caution must be applied in interpreting them, because of limitations in the selection methods and data analysis.*

A major concern is how the cases of CP were selected, i.e. selection bias (affecting the denominator of mortality rates). The dataset from which the sample was drawn comprised 182 263 individuals with developmental disability being evaluated annually, for receipt of services, by a 200-item questionnaire, the Client Development Evaluation Report (CDER). CP was identified if three items of the questionnaire (severity, type, and location of CP) 'indicated presence of [CP]'. This 'case definition' was tautological, and lacked specific inclusion and exclusion criteria. It remains unclear how CP itself was defined and how, for each item, the category 'other/unspecified' was used. If two items were present, for example, did the authors ignore CP as a diagnosis, even though both items purported to be descriptors of CP?

The dataset comprised those who were entitled to receive services from the State of California. Several biases must therefore be considered. The authors acknowledged that those receiving services might have more severe CP than those not entitled, but also very severe cases who died early may never have received services. The approach to case ascertainment was unlikely to be as comprehensive in detecting cases of CP as a prospective population-based CP register.

In the Introduction, the authors cited Badawi et al.'s case definition of CP: 'a group of motor disorders of central origin... As generally understood there must be motor impairment, and this impairment must stem from a malfunction of the brain (rather than spinal cord or muscles)... [the brain malfunction] must be non-progressive and it must be manifest early in life'[2]. If the operational case definition of CP, implicitly or explicitly, correctly included non-progression, classifying the sequelae of a progressive brain tumour as non-progressive CP might have been encouraged. This misclassification would confer entitlement to services that might otherwise be forgone.

A further concern is information bias, namely classification of the 'cause of death' (affecting the numerator of mortality rates). Although the authors did not explicitly identify which component of the Cause of Death statement from the death certificate was analysed, presumably it was the Underlying Cause of Death (i.e. 'the disease or injury which initiated the train of morbid events leading directly to death'[3]). According to international convention, when only one element is reported in official mortality statistics, it is the Underlying Cause of Death – as derived from the Cause of Death statement by internationally agreed coding rules (International Classification of Disease [ICD] 9th revision)[3].

Generally, Strauss et al. used the non-specific term 'cause of death' throughout. This term includes the Underlying Cause of Death, Intermediate (Other Antecedent) Cause(s) of Death, Direct (Immediate) Cause of Death, and Contributory Cause(s) of Death. The term Underlying Cause of Death is used for the first time in the penultimate paragraph of the paper (and related table). They stated that 724 (30%) of the 2416 deaths of those aged over 14 years had a 'cause of death' (presumably Underlying Cause of Death) 'uninformative for our purposes'. These comprised infantile CP, congenital anomalies or undefined causes! While respiratory infection may well be the Immediate Cause of Death in people with CP, we would expect CP itself to be the Underlying Cause of Death in a substantial proportion. In our research (282 deaths), this was 34%[4]. Indeed, Strauss et al.'s data may well have included an approximately similar proportion, but we can only deduce that less than 30% of deaths had CP as the Underlying Cause of Death (because that proportion included congenital anomalies or undefined causes). Strauss et al. hypothesised that all 30% might have had respiratory disease as the Underlying Cause of Death.

In the Discussion, Strauss et al. reported their analysis of a second and separate data source, the National Health Interview Survey data for Underlying Cause of Death (+ Contributory Cause[s] of Death), because 'we do not have access to multiple-cause-of-death data which can be linked to our own'. The nature of this data source or the denominator population size were not revealed, except that the data were extracted for Californians, aged 18 years and over, for 1986 to 1994 (9-year period) with 'a reference to [CP]'. In a footnote to the table, Strauss reported that '7% [had CP] cited as the underlying cause', much lower than our observation of 34% (for age 0 to 33 years, all causes)[4]. Their case definition included ICD-9 codes 333.2, 333.7, 342–344, which was reasonably comparable to ours of 343–344 (we had no deaths for the other codes). They 'identified the 401 individuals whose death certificate included a reference to [CP]'. Relating this to the 4028 individuals stated in the Method as dying during the study period [1986 to 1995, 10-year period]', this gives approximately 10 to 11% of deaths, i.e. much lower than the 55% of deaths that we reported for any mention of CP (not just as Underlying Cause of Death or Contributory Cause[s] of Death)[4].

A further analytical concern is that the authors stated that they calculated the excess mortality as standardised mortality ratios (SMRs). An SMR is a summary measure combining several observed age-specific numbers expressed as a ratio to the expected number of deaths if the age-specific rates in a standard population applied. The authors' tabulated 'SMRs' were not apparently summary values; rather each was a simple ratio of the observed to the expected number of deaths within a single age-group.

We therefore assume that these were age-specific mortality ratios, not the summary measure of the standardised mortality ratio. If the authors did calculate SMRs, as could be inferred from the table footnotes, they did not disclose the age-specific class intervals used to derive these summary measures.

Despite airing these concerns about method and interpretation, we do not wish to diminish the potential importance of specifying excess causes of death in CP. The authors were correct in indicating that many questions have been left unanswered. Indeed, their results must be interpreted with considerable caution, and verified in other studies before being used, for example, to adjust predictive models of life expectancy for those with CP.

Dr Gillian Maudsley
Senior Lecturer in Public Health Medicine
Department of Public Health
Whelan Building
Quadrangle
The University of Liverpool
Liverpool, L69 3GB, UK

Peter O D Pharoah
Emeritus Professor of Public Health
Department of Public Health
Muspratt Building
The University of Liverpool
Liverpool, L69 3GB, UK

References

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2. Badawi N, Watson L, Petterson B, Blair E, Slee J, Haan E, Stanley F. (1998) What constitutes cerebral palsy? *Developmental Medicine & Child Neurology* **40:** 520–7.
3. World Health Organization. (1977) *Manual of the International Classification of Diseases, Injuries and Causes of Death. Volume 1. 9th revision*. London: HMSO.
4. Maudsley G, Hutton JL, Pharoah POD. (1999) Cause of Death in cerebral palsy: a descriptive study. *Archives of Disease in Childhood* **81:** 390–4.

'Strauss replies'

SIR–*We were surprised that Maudsley and Pharoah chose to write to the editor rather than to us. Had they done so we could have resolved the issues quickly without troubling the reader with some rather tedious details.*

Their 'analytical concern' boils down to asking whether we used the standard 5-year intervals when calculating our SMRs. Answer: Yes.

Concerning the 'selection bias': (1) The supposedly tautological definition of CP: as explained in the article, we relied on the assessments from a team of pediatricians, developmental psychologists, and other professionals. (2) If two of the three items were scored as CP but one was not, did we count the case as being CP? Answer: No. We stated that 'A CDER evaluation was defined as being one of CP if all three items indicated presence of CP.' Our aim was to be conservative in identifying cases of CP. For the record, only about one person in 500 in our database fell into this 'two out of three' category. (3) As we explained, all children with developmental disabilities in California are entitled to services. We are aware, of course, that a child who died in, say, the first week of life may not have been assessed, and thus not be included in our database. This is doubtless true of any database, including Maudsley and Pharoah's. (4) Maudsley and Pharoah suggest that children with brain tumors may be deliberately misclassified as having CP instead, so as to make them eligible for services. But it is the cognitive and/or developmental disabilities that make the children eligible for services, not the designation of CP.

Regarding the cause of death information: what we have is the underlying cause, as Maudsley and Pharoah say. We were well aware of the limitations of this data. It was feasible for Maudsley and Pharoah to obtain more detailed information on their 282 deaths, but this was hardly practical for the 4028 CP deaths in our database.

David Strauss
Department of Statistics
University of California
Riverside, CA, USA

Notice

UK Epilepsy Drug Trial – Invitation to Participate
The Place of New Drugs in the Treatment of Epilepsy

The past decade has seen the licensing of five new antiepileptic drugs in the United Kingdom, and more are likely to follow in the near future. Unfortunately, the clinical trials required to obtain a licence for a new drug do not answer important practical questions about how and when we should use them. In particular, studies that compare new versus the standard drugs are largely lacking. Because of this, the NHS Research and Development Health Technology Assessment Programme is sponsoring a pragmatic study that will compare carbamazepine and valproate as standard antiepileptic drugs with recently licensed competitors, gabapentin, lamotrigine, and topiramate. It will compare monotherapy with these drugs across a range of clinical, psychosocial, and health economic outcomes, with the aim to recruit 3000 patients in the United Kingdom within the next 3 years. Because epilepsy has its highest incidence in childhood and adolescence, it is very important that these groups are represented in the study.

Many of you may have already received information on this study. If you have not and would like to do so, please contact: SANAD Study Office, University Department of Neurological Science, The Walton Centre for Neurology and Neurosurgery, Lower Lane, Liverpool L9 7LJ. Tel: 0151 529 5464, Fax: 0151 529 5466. E-mail: bessan-p@wcnn.co.uk