

# 논문의 비판적 검토(critical appraisal): 실습

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## 학습목표

학술논문의 비판적 검토(critical appraisal)에 관하여, 그 필요성을 이해하고, 수행과정에서 감안하여야 할 구성요소를 파악한다.

## 실행목표

역학적 연구의 주요 연구설계인 환자-대조군 연구와 코호트 연구 방식으로 수행되어 각각 *BMJ*에 수록된 논문을 읽고, 비판적 검토 체크사항 (checklists)에 따라 평가한다.

## 註

이 강의록은 "Evidence Based Health Care Workbook: understanding research For individual and group learning Based on the book *How to Read a Paper*. Greenhalgh T, Donald A. BMJ Publishing Group, 2000 London"을 근간으로 하여 작성되었음; 환자-대조군 연구와 코호트 연구의 기본 개념은 <http://www.bmj.com/epidem/epid.html> 사이트에 수록된 *Epidemiology for the Uninitiated, Fourth Edition*을 번역하였음

## I. 들어가는 말

의학연구의 길에 처음 접어든 사람이거나 이미 상당한 경력을 쌓았다고 생각하는 연구자에게나, 현재 수행하고 있는 연구가 '올바른 방향으로 제대로 진행'되고 있는지 검토하는 일은 중요하다 하겠다. 이 지적이 옳다는 점에는 아무도 이의를 제기하기 않겠지만, 올바른 방향으로 제대로 진행된다는 것이 무엇을 의미하는지에 대해서는 견해가 다를 수 있다.

연구진행 자체가 적절한지 실시간(real time)으로 파악하는 일은 매우 어렵기 때문에, 그 결과물으로써 적절성을 평가하는 우회로를 택하고자 한다. 즉 연구의 결과물인 논문을 평가함으로써 그 논문이 나오기까지의 연구진행이 적절했었는지를 파악하려는 것이다. 이러한 과정을 공식적으로는 논문의 비판적 검토(critical appraisal)라 통칭하며, 이미 언급한 대로 연구자의 필수 덕목이다.

논문의 비판적 검토의 중요성이 인식되고, 심지어는 그러한 용어 자체가 친밀하게 느껴지게 된 데는, 1980년대 이후 Evidence based medicine (EBM)의 유행에 힘입은 바 크다. 즉 환자의 진료는 의학적 연구 등에서 얻어진 객관적 증거를 근간으로 하여야 한다는 주장이다. 객관적 증거로 인정받기 위해서는 해당 논문의 객관적 타당성이 보장되어야 하는데, 그러한 과정이 논문의 비판적 검토에 해당하는 것이다. 물론 논문의 비판적 검토는 EBM 이전에도 의학연구자라면 누구나 알고 있는 개념을 보다 공식화, 보편화시킨 것에 지나지 않는다.

여기에서는 역학적 연구에 초점을 맞추어, 흔히 수행하는 연구설계인 환자-대조군 연구(case-control studies)와 코호트 연구(cohort studies)를 중심으로 기술하고자 한다. 다음에서는 두 연구설계의 기본 개념을 간단히 소개

하고, 해당 연구의 비판적 검토에서 고려하여야 하는 점을 정리한다. 이후에 대표적 의학 학술지인 *BMJ*에 실린 두 편의 연구논문을 중심으로, 실제 비판적 검토를 수행해 보도록 한다.

## II. 환자-대조군 연구와 검토 사항(checklists)

### 1. 기본 개념

발생이 흔하지 않은 질환(실제로는 전염병 유행 같이 발생이 폭발적으로 일어나지 않는 대부분의 만성질환이 다 해당된다.)의 위험요인을 규명하는데 필수적인 연구설계이다. 연구에 소요되는 시간이나 경비가 이후 언급할 코호트 연구에 비하여 매우 적기 때문에 선호되고 있지만, 연구결과의 타당성을 보장하기 위한 연구자의 노력은 경비 절감 부분 이상 소요된다.

환자-대조군 연구에서는 해당 질병이 발생한 환자를 확인한 후 과거 그들이 위험요인에 노출되었는지 조사하여, 대조군(질병이 없는)과 비교한다. 대응위험도(odds ratios)가 추정되며, 분석 단계에서 통계적 방법으로 교란변수의 영향을 보정할 수 있다. 간혹은 교란변수 값이 동일하도록 환자군과 대조군을 짝짓기(matching)하기도 한다.

환자-대조군 연구의 첫 단계인 환자군 선정에서는 적절하고도 명확한 환자의 정의가 필수적이다. 또한 환자군을 선정할 때 비뚤림이 발생하지 않도록 주의하여야 하는데, 예를 들어 전립선비대증 연구에서 환자군을 병원 입원 환자 중에서만 선정할 경우, 질병 유무나 중증도가 아닌 다른 변수(사회경제적 요인과 같은)에 의한 영향을 받을 수 있다. 한편 환자 중에서도 유병자가 아닌 신환(incident cases)이 선호되는데, 유병(prevalence) 여부는 질병 발생 위험에 영향을 주는 요인뿐 아니라 유병 기간에 영향을 주는 요인에 의해서도 결정되기 때문이다. 그리고 장기간 유병 환자의 경우 발병 전의 위험요인 파악이 어려운데, 환자의 기억에 의존하여 자료를 수집하는 경우 더욱 그 가능성이 높다.

대조군의 선정은 환자군 선정에 비하여 어려운데, 이상적으로 대조군은 두 가지 조건을 만족하여야 한다. 첫째 이들의 위험요인이나 교란변수에 대한 폭로 상태가 본 연구에서 환자가 될 가능성이 있는(at risk), 그리고 발병 시 환자군으로 선정될 가능성이 있는 인구집단을 대표하여야 한다. 이 인구집단은 다시 말하면 대상 질병은 없지만, 일단 발병할 경우 환자군으로 선정될 사람을 지칭한다. 둘째 대조군의 폭로 상태가 환자군에서와 같은 조건으로 측정되어야 한다.

흔히 대조군은 일반 인구 중에서 선정하는데 환자군이 될 가능성이 있는 인구집단을 대표하기 쉽다는 장점이 있다. 그러나 폭로 상태 측정에 있어 환자군과 비교성이 적을 가능성이 있는데, 개인적 회상에 의하여 파악하는 경우에 특히 그렇다. 환자군은 자기 질병을 일으킨 요인을 찾는 데 민감하여 과거 기억을 잘 하는 경향이 있기 때문이다.

폭로 측정의 비교성을 유지하기 위하여, 다른 질병 환자를 대조군으로 선정하는 경우가 있는데, 연구 목적을 뚜렷이 밝히지 않은 경우 가능하다. 그러나 이때는 대표성이 없다는 문제가 발생한다. 예를 들어 방광암과 흡연에 대한 환자-대조군 연구에서 대조군을 호흡기 내과에서 선정하면 엉뚱한 결과가 나올 것이다. 따라서 타 질환 환자를 대조군으로 쓰려면 가능한 많은 질병을 포함하는 것이 좋다.

대조군을 위의 두 가지 모두 선정하여 연구결과 해석에 도움이 되는 경우도 있다. 예를 들어 phenoxy herbicides인 2,4-D와 2,4,5-T과 soft tissue sarcoma간의 관련성이 의심되었는데 일반 인구를 대조군으로 사용한 연구는 회상의 차이 때문에 위험도가 과대평가되고, 다른 암(soft tissue sarcoma보다 herbicide와 관련성이 높은) 환자를 대조군으로 사용한 연구는 위험도가 과소 평가되는 경향이 있다. 따라서 실제 진짜 위험도는 그 중간 어디쯤엔가

위치할 것이다.

총 대상자 수가 일정한 경우, 동수로 뽑는 것이 가장 효과적이지만, 환자군의 숫자가 제한된 경우 환자 1명당 2명 이상의 대조군을 선정하기도 한다. 그러나 law of diminishing returns에 따라 4를 넘어가면 별 소용이 없다.

위험요인에의 폭로 여부는 개인적 회상으로 파악하는데 자기 기입 설문지나 면접조사로 파악한다. 그 정보의 타당성은 경우에 따라 다른데 과거에 살았던 곳이나 직업 등은 잘 기억하는 반면 장기간에 걸친 식이 습관 등은 상대적으로 신뢰도가 떨어진다. 가끔은 과거 기록에서 폭로 여부를 파악하기도 하는데, sinusitis와 이후 multiple sclerosis 발생 위험에 대한 연구에서, 과거 병력을 의무기록에서 파악한 예가 있다. 그 기록이 상당 부분 완전하다면 기억에 의존한 방법보다 정확할 것이다.

한편 장기간 폭로를 반영하는 생물학적 표지자가 활용되기도 한다. 결핵 예방에서 BCG 백신의 효과를 보는 아프리카 연구는 상박의 흉터를 이용하였다. 그러나 생물학적 표지자는 이후 질병 발생 과정에서 변화되어서는 안 된다. 예를 들어 심근경색증 이후에 측정된 혈중 콜레스테롤 농도는 심근경색증 발병 이전의 수준을 정확히 반영할 수 없다.

## 2. 검토 사항

### A. 연구의 결과가 타당하며, 비뚤림(bias)가 최소화되었는가?

#### 1. 명확하고 초점이 뚜렷한 질문을 가지고 있는가(PEO)?

- 인구집단(Population)
- 명시된 특정 기간 동안의 위험요인 폭로(Exposure)
- 결과(Outcomes)

2. 저자들이 연구한 결과 또는 질병이 매우 드물거나 희귀한가? (폭로가 희귀하다는 뜻은 아님; 희귀한 결과를 연구하는 경우에만 환자-대조군 연구의 정당성을 인정할 수 있음)

3. 환자-대조군 연구설계가 인구집단에 근거(population based; 논리적 설득력 강함)하였는가?

4. 관심 대상 결과(질병) 이외에, 연구 개시 시점에 두 집단(환자군과 대조군)의 주요 요인(예를 들어 성별, 연령, 사회경제적 요인) 분포가 유사한가?

5. 짝짓기를 하였다면 환자 1명 당 대조군이 4명 이하인가?

### B. 연구결과는 어떠한가?

#### 5. 위험요인 폭로의 영향은 어느 정도인가?

- 결과로 파악하였던 사건은 무엇이며, 측정지표는 무엇인가? (대응위험도인데 질병이 희귀한 경우 상대위험도와 비슷함)

6. 폭로 효과 지표 추정치는 얼마나 정밀한가?

● 신뢰 구간 또는  $p$  값은?

C. 연구결과가 얼마나 관련(relevance) 있는가?

7. 연구 대상자가 내가 관심 있는 인구집단과 전혀 달라 본 연구결과가 아무 도움도 되지 않는가?

3. 예제 논문: casecontrol.pdf (총 5쪽)

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998; **317**: 1554-1558



# Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study

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BMJ 1998;317:1554-8

## Abstract

**Objective** To identify intrapartum predictors of newborn encephalopathy in term infants.

**Design** Population based, unmatched case-control study.

**Setting** Metropolitan area of Western Australia, June 1993 to September 1995.

**Subjects** All 164 term infants with moderate or severe newborn encephalopathy; 400 randomly selected controls.

**Main outcome measures** Adjusted odds ratio estimates.

**Results** The birth prevalence of moderate or severe newborn encephalopathy was 3.8/1000 term live births. The neonatal fatality was 9.1%. Maternal pyrexia (odds ratio 3.82), a persistent occipitoposterior position (4.29), and an acute intrapartum event (4.44) were all risk factors for newborn encephalopathy. More case infants than control infants were induced (41.5% and 30.5%, respectively) and fewer case infants were delivered by caesarean section without labour (3.7% and 14.5%, respectively). Operative vaginal delivery (2.34) and emergency caesarean section (2.17) were both associated with an increased risk. There was an inverse relation between elective caesarean section (0.17) and newborn encephalopathy. After application of a set of consensus criteria for elective caesarean section only three (7%) eligible case mothers compared with 33 (65%) eligible control mothers were sectioned electively. Of all the case infants, 113 (69%) had only antepartum risk factors for newborn encephalopathy identified; 39 (24%) had antepartum and intrapartum factors; eight (5%) had only intrapartum factors; and four (2%) had no recognised antepartum or intrapartum factors.

**Conclusions** The causes of newborn encephalopathy are heterogeneous and many relate to the antepartum period. Elective caesarean section has an inverse association with newborn encephalopathy.

Intrapartum hypoxia alone accounts for only a small proportion of newborn encephalopathy. These results question the view that most risk factors for newborn encephalopathy lie in the intrapartum period.

## Introduction

Previous studies of newborn encephalopathy have focused almost exclusively on the intrapartum causes of "hypoxic ischaemic encephalopathy".<sup>1-7</sup> The contribution of intrapartum events to newborn encephalopathy remains unclear. We report the intrapartum findings from the Western Australian case-control study of newborn encephalopathy.<sup>8</sup>

## Subjects and methods

The subjects and methods are as reported in the accompanying paper.<sup>8</sup>

## Results

### Intrapartum period

Maternal pyrexia, a persistent occipitoposterior position, and an acute intrapartum event were all labour related events associated with a significantly increased risk of newborn encephalopathy (table 1). Only nine of the 18 affected infants and none of the nine control infants whose mothers had experienced pyrexia had a pathogenic organism isolated from mother or baby. A prolonged interval from rupture of membranes to delivery, abnormalities in blood pressure, a nuchal cord, cord prolapse, and shoulder dystocia were associated with a non-significantly increased risk.

### Onset of labour and final mode of delivery

The final mode of delivery is determined by the delivery plan and response to intrapartum events. As the delivery plan could not be determined onset of labour was investigated as a surrogate (table 1). The same proportion of cases and controls had spontaneous onset of labour. More case infants than control infants, however, were induced and fewer case infants were delivered by caesarean sections without labour.

Overall, a similar proportion of case and control infants were delivered by caesarean sections (23% (38) and 24% (96), respectively). Relative to spontaneous vaginal delivery, instrumental vaginal delivery and emergency section were associated with over a twofold increased risk of encephalopathy. Only 2.4% (four) affected infants compared with 14.5% (58) of control infants were delivered by elective section, defined as one planned at least 24 hours before the procedure (adjusted odds ratio relative to spontaneous vaginal delivery 0.17; 95% confidence interval 0.05 to 0.56). This inverse relation was not explained by social factors, including health insurance status, as these had been adjusted for. The documented indications for elective sections among case and control infants are shown in table 2; previous caesarean section was the most common.

To ascertain whether different risk factor profiles explained the differences in proportion of emergency and elective caesarean sections, 14 practising consultant obstetricians from Perth were asked to develop a set of criteria which would lead them to recommend an elective section at term in the interest of the baby. The consensus, which was developed without knowledge of the study results, comprised intrauterine growth restriction, malpresentation, abnormal antepartum cardiotocography, two previous sections, macrosomia with diabetes or gestational diabetes, active herpes, and a previous difficult labour. When we applied these consensus criteria to mothers of case and control infants (table 3) eligible mothers of case infants were 24 times less likely (unadjusted odds ratio relative to spontaneous vaginal delivery 24.2; 6.61 to 90.1) than eligible

mothers of control infants to have been sectioned electively. Nearly 40% of the eligible case infants were eventually delivered by an emergency section and nearly 20% were delivered instrumentally or by vaginal breech delivery. The consensus criteria met by eligible mothers are summarised in table 4. This shows that even in the group that met the consensus criteria there was a difference in antepartum risk factor profiles between cases and controls.

#### Other intrapartum factors

The presence of an abnormal intrapartum cardiotocogram, meconium stained liquor, and fetal distress are usually considered to reflect intrapartum hypoxia and were not included in the adjusted analyses as they were likely to be along a causal pathway for, or the first signs of, newborn encephalopathy or were markers of encephalopathy. Inclusion of these variables in the adjusted analysis would have masked the effects of other variables that were working through them. Half the affected infants had intrapartum cardiotocography performed compared with 30% of control infants. The cardiotocogram was described as abnormal in 61% of affected infants compared with 37% of control infants (unadjusted odds ratio 4.43; 1.81 to 10.85). Meconium was described more commonly in case infants than control infants (33% *v* 12%; 3.72; 2.33 to 5.95) and grade III meconium in particular was much more common in case infants (13% *v* 1.0%; 16.7; 5.76 to 50.0). Finally, fetal distress during labour was recorded by the midwife more often in case infants than control infants (21% *v* 8%; 3.16; 1.84 to 5.43). For the same reason we did not include immediate characteristics of the newborn (table 5) in the adjusted analysis.

#### Contribution of possible intrapartum hypoxia

In an attempt to estimate the proportion of infants who had been exposed to possible intrapartum hypoxia we used the following modified criteria: presence of an abnormal intrapartum cardiotocogram or abnormal fetal heart rate on auscultation or fresh meconium in labour, or both, together with a 1 minute Apgar score of less than 3 and a 5 minute Apgar score of less than 7.<sup>9</sup> Cord pH measurements were not included because they were performed so infrequently. Thirty one affected infants (19%) and two control infants (0.5%) fulfilled these criteria. A further 16 cases did not strictly fulfil the definition, but there was evidence that they had experienced a significant intrapartum event which may have been associated with intrapartum hypoxia (for example, breech presentation, birth before arrival at hospital, head stuck, Apgar scores not measured). Therefore, a total of 47 case infants (29%) had evidence of having experienced intrapartum hypoxia. Only seven of these (4% of all cases), however, fulfilled the criteria of possible intrapartum hypoxia in the absence of preconceptional or antepartum abnormalities. Four case infants (2%) had no recognised antepartum risk factors or evidence of intrapartum hypoxia and 113 (69%) had only antepartum factors identified (figure 1). Only 15 of these 47 case infants met the consensus eligibility criteria for an elective caesarean section.

**Table 1** Risk factors for newborn encephalopathy present in intrapartum period and adjusted for factors before birth and antepartum

Risk factor	No (%) of cases (n=164)	No (%) of controls (n=400)	Unadjusted odds ratio	Adjusted odds ratio* (95% CI)
<b>Occipitoposterior presentation:</b>				
No	147 (89.6)	385 (96.2)	1†	1†
Yes	17 (10.4)	15 (3.8)	2.97	4.29 (1.74 to 10.54)
<b>Maternal pyrexia (≥37.5°C):</b>				
No	146 (89.0)	391 (97.8)	1†	1†
Yes	18 (11.0)	9 (2.2)	5.34	3.82 (1.44 to 10.12)
<b>Acute intrapartum event‡:</b>				
No	151 (92.1)	395 (98.8)	1†	1†
Yes	13 (7.9)	5 (1.2)	6.80	4.44 (1.30 to 15.22)
<b>Membrane rupture to delivery interval &gt;12 hours:</b>				
No	132 (80.5)	347 (86.7)	1†	1†
Yes	32 (19.5)	53 (13.2)	1.59	1.31 (0.69 to 2.47)
<b>Blood pressure abnormalities:</b>				
No	154 (93.9)	383 (95.8)	1†	1†
Yes	10 (6.1)	17 (4.2)	1.46	1.78 (0.61 to 5.15)
<b>Nuchal cord:</b>				
No	142 (86.6)	369 (92.2)	1†	1†
Yes	22 (13.4)	31 (7.8)	1.84	1.81 (0.85 to 3.86)
<b>Cord prolapse:</b>				
No	163 (99.4)	399 (99.8)	1†	1†
Yes	1 (0.6)	1 (0.2)	2.45	4.71 (0.21 to 105.02)
<b>Onset of labour:</b>				
Spontaneous	90 (54.9)	220 (55.0)	1†	1†
Induced	68 (41.5)	122 (30.5)	1.36	0.97 (0.57 to 1.68)
None	6§ (3.7)	58 (14.5)	0.25	0.17 (0.06 to 0.49)
<b>Mode of delivery:</b>				
Spontaneous vaginal	49 (29.9)	261 (65.3)	1†	1†
Induced vaginal	32 (19.5)	80 (20)	1.31	1.10 (0.55 to 2.18)
Instrumental vaginal	42 (25.6)	62 (15.5)	2.23	2.34 (1.16 to 4.70)
Elective caesarean section	4 (2.4)	58 (14.5)	0.23	0.17 (0.05 to 0.56)
Emergency caesarean section	34 (20.7)	38 (9.5)	2.94	2.17 (1.01 to 4.64)
Breech manoeuvre	3 (1.8)	1 (0.3)	9.86	1.54 (0.10 to 25.14)
<b>Shoulder dystocia:</b>				
No	155 (94.5)	393 (98.3)	1†	1†
Yes	9 (5.5)	7 (1.7)	3.26	3.0 (0.77 to 11.67)
<b>General anaesthesia:</b>				
No	146 (89.0)	389 (97.2)	1†	1†
Yes	18 (11.0)	11 (2.8)	4.40	3.08 (1.16 to 8.17)
<b>Epidural anaesthesia:</b>				
No	145 (88.4)	331 (82.8)	1†	1†
Yes	19 (11.6)	69 (17.2)	0.64	0.51 (0.26 to 1.02)

\*Adjusted for maternal age, parity, employment status, health insurance status, race, family history of epilepsy and other neurological disease, infertility treatment, hypertension, height, thyroid disease, pre-eclampsia, moderate or severe bleeding, viral illness, alcohol consumption, gestational age, centile birth weight, infant sex, appearance of placenta, late or no antenatal care, hospital of delivery, and plurality. †Baseline comparison group. ‡Haemorrhage (n=7), maternal convulsions (n=2), rupture of uterus (n=1), snapped cord (n=1), and birth of baby before arrival at obstetric facility (n=2). §Includes two women who had emergency caesarean sections before onset of labour.

**Table 2** Indications for elective caesarean section documented by midwife according to whether baby had newborn encephalopathy (cases) or not (controls)

Indication	No delivered by caesarean
<b>Controls (n=58)</b>	
Previous caesarean section	32
Malpresentations	9
Previous difficult labour	4
Intrauterine growth retardation	2
Placenta previa	2
Other reasons*	9
<b>Cases (n=4)</b>	
Two previous caesarean sections	2
One previous caesarean section	1
Intrauterine growth retardation	1

\*One each of antepartum fetal tachycardia, active herpes infection, nephrotic syndrome, cephalopelvic disproportion, pre-eclampsia with inflammatory bowel syndrome, oligohydramnios, macrosomia, maternal request, reason not given.

**Table 3** Details of onset of labour and final mode of delivery in cases (babies with newborn encephalopathy) and controls by eligibility for elective caesarean section according to consensus criteria.\* Values are numbers (percentages) of subjects

Detail	Cases		Controls	
	Elective section candidates (n=43)	Others (n=121)	Elective section candidates (n=51)	Others (n=349)
<b>Labour onset:</b>				
Spontaneous	19 (44.2)	71 (58.7)	9 (17.7)	211 (60.5)
Induced	20 (46.5)	48 (39.7)	9 (17.7)	113 (32.4)
None	4† (9.3)	2 (1.7)	33 (64.7)	25 (7.2)
<b>Final mode of delivery:</b>				
Elective caesarean	3 (7.0)	1 (0.8)	33 (64.7)	25 (7.2)
Non-elective caesarean	17 (39.5)	17 (14.1)	7 (13.7)	31 (8.9)
Instrumental and breech	8 (18.6)	37 (30.6)	4 (7.8)	59 (16.9)
Induced vaginal	8 (18.6)	24 (19.8)	5 (9.8)	75 (21.5)
Spontaneous vaginal	7 (16.3)	42 (34.7)	2 (3.9)	159 (45.6)

\*Eligibility defined by consensus opinion of 14 obstetricians. Consensus list was intrauterine growth retardation, malpresentation, abnormal antepartum cardiotocogram, two previous caesarean sections, macrosomia with diabetes or gestational diabetes, active herpes, and previous difficult labour.

†Includes two women who had emergency caesarean sections before onset of labour.

**Table 4** Consensus criteria met by mothers of cases (babies with newborn encephalopathy) and controls eligible for elective caesarean section.\* Values are numbers (percentages) of subjects

Consensus criteria*	Eligible cases (n=43)	Eligible controls (n=51)
Predicted infant weight <3rd centile	21 (48.8)	5 (9.8)
Abnormal antepartum cardiotocogram	14 (32.6)	8 (15.7)
Breech and other malpresentations	9 (20.9)	21 (41.2)
Two previous caesareans	3 (7.0)	12 (23.5)
Previous difficult labour	0 (0)	4 (7.8)
Gestational diabetes and macrosomia	1 (2.3)	0 (0)
Active herpes	0 (0)	2 (3.9)

\*These criteria are not mutually exclusive.

## Discussion

Our results indicate that intrapartum hypoxia alone accounts for only a small proportion of cases of newborn encephalopathy, and elective caesarean section had an unexpected inverse association with newborn encephalopathy.

### Role of intrapartum hypoxia

Although 29% of affected infants experienced events traditionally indicative of birth asphyxia, it does not necessarily follow that asphyxia was the primary cause of the encephalopathy. While some intrapartum factors may be single causes—that is, a previously normal baby who becomes encephalopathic in labour (fig 2, pathway 1)—this was an uncommon scenario in our study (see fig 1). Other factors may be on a causal pathway that starts before birth but which includes intrapartum hypoxia as a contributor (figure 2, pathway 2). For example, growth restriction alone is associated with newborn encephalopathy<sup>8</sup> and exposure to labour may compound that damage.<sup>10</sup> A further possibility is that the intrapartum factors are merely markers of damage associated with adverse events before birth (fig 2, pathway 3). Abnormality on a cardiotocogram, meconium stained liquor, low Apgar scores, or the need for active resuscitation may simply reflect previous neurological compromise.<sup>11</sup>

A very small proportion of infants had no recognised antepartum risk factors nor evidence of intrapartum hypoxia, and it remains unclear as to when their encephalopathy started and what caused it.

Over two thirds of affected infants had only antepartum factors identified. Together these two groups represent over 70% of cases among which there was no evidence of adverse intrapartum events. This points to the antepartum period being of prime aetiological importance in most cases of newborn encephalopathy.

### Infection

Maternal pyrexia in labour was a significant risk factor, confirming our previous finding.<sup>12</sup> Prolonged interval between rupture of membranes and delivery, a risk factor for ascending infection, was more common in cases compared with controls but not significantly so. Chorioamnionitis is of current interest as a cause of cerebral palsy in both term<sup>13</sup> and preterm<sup>14</sup> infants. The mechanisms of fetal damage, however, are not known but could include cerebral sepsis, hyperthermia, or action via inflammatory mediators.<sup>15</sup>

### Caesarean section

The most striking finding relates to mode of delivery. These data suggest an important inverse association between elective caesarean section and newborn encephalopathy. There are several possible explanations for this finding. Chance alone is an unlikely explanation, as shown by the 95% confidence interval, although mode of delivery was not one of the initial study hypotheses.<sup>12</sup> The results are also unlikely to be due to biased selection of control subjects. The control

**Table 5** Immediate characteristics of babies with encephalopathy (cases) and controls. Values are numbers (percentages) of subjects

Characteristic	Cases (n=164)	Controls (n=400)
<b>Apgar at 1 minute:</b>		
<3	50 (30.5)	3 (0.7)
3-6	46 (28.1)	37 (9.2)
>6	67 (40.8)	359 (89.7)
Missing	1 (0.6)	1 (0.2)
<b>Apgar at 5 minutes:</b>		
<3	14 (8.5)	0
3-6	40 (24.4)	5 (1.2)
>6	108 (65.9)	394 (98.5)
Missing	2 (1.2)	1 (0.2)
<b>Onset of respiration:</b>		
≤2 minutes	83 (50.6)	373 (93.2)
>2 minutes	68 (41.5)	15 (3.7)
Not established	6 (3.7)	0
Missing	7 (4.2)	12 (3.0)
<b>Airway resuscitation:</b>		
None	30 (18.3)	283 (58.2)
Suction alone	15 (9.1)	82 (20.5)
Oxygen	29 (17.7)	49 (12.2)
Bag and mask	35 (21.3)	30 (7.5)
Intubation	44 (26.8)	4 (1.0)
Intubation and CPR*	10 (6.2)	0
Missing	1 (0.6)	2 (0.5)
<b>Cord pH:</b>		
Not measured	135 (82.4)	391 (97.7)
<7.0	5 (3.0)	0
7.0-7.1	14 (8.5)	2 (0.5)
≥7.2	9 (5.5)	6 (1.5)
Missing	1 (0.6)	1 (0.2)
<b>Birth trauma:</b>		
Present	17 (10.4)	0

\*Cardiopulmonary resuscitation.

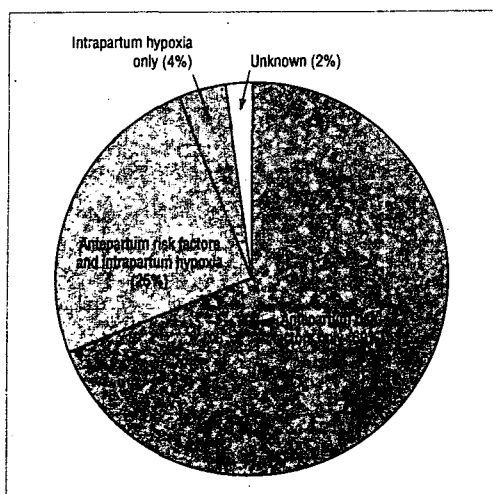


Fig 1 Distribution of risk factors for newborn encephalopathy

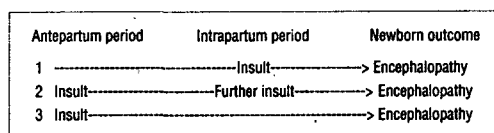


Fig 2 Theoretical scenarios for timing of neurological insult in newborn encephalopathy

subjects were randomly selected and their final mode of delivery and all 21 other characteristics of pregnancy, labour, and infant available for comparison were the same as for all term live births in Western Australia during the study period.<sup>16</sup> There was no evidence of case selection bias as all affected infants were included and none died before transfer.<sup>8</sup> We therefore conclude that our findings are real.

A vital distinction, not made in most other studies, is the differentiation between elective and non-elective sections.<sup>2 12 17 18</sup> Had we failed to make this distinction we would have concluded that caesarean section had no effect on the risk of newborn encephalopathy. When we applied the eligibility criteria for elective sections we found that eligible case infants were more than 20 times less likely to be delivered by elective section than eligible control infants. The reasons for the apparent differences in the management of labour in the cases and controls are undoubtedly complex and may reflect genuine differences (see table 4). Unrecognised high risk features, alternatives to the consensus view, women's choice of vaginal delivery, or perhaps some undefined factors which led a pregnancy to result in a baby with encephalopathy may also have operated to affect the management of delivery. As the definition of an elective caesarean section was one in which there were 24 hours between the decision and delivery, it is also possible that some of these women had been booked for an elective section which they did not receive because they went into labour. On close review of the eligible cases, however, a maximum of only 20% could possibly fall into this category.

It is of note that even in those women not meeting the consensus criteria for elective section, mothers of control infants were electively sectioned much more commonly than mothers of case infants. Furthermore,

eligible mothers of case infants did not avoid operative and instrumental delivery but had emergency rather than elective procedures. Non-elective sections involve inherently more operative and postoperative risk, reflected in the lower maternal morbidity after elective sections.<sup>19</sup> In addition, the baby delivered by a non-elective section has usually been exposed to the stresses of labour, and this may have an independent impact on outcome.

Elective caesarean sections may exert their apparent beneficial effects by avoiding some of the intrapartum risk factors for encephalopathy. For example, elective sections prevent exposure to post-maturity, persistent occipitoposterior position, intrapartum maternal pyrexia, and catastrophic events in labour. It may be the avoidance of these factors other than caesarean section per se which contributes to its apparent benefit.

We readily recognise that there is no "correct rate" of elective caesarean sections, but it is pertinent to ask whether women who would benefit most are being identified and given access to this method of delivery. It is not possible to say from this observational study whether elective section would have actually changed the outcome in any of the cases, but it is an obvious question and one worthy of further investigation. As a trial to answer this question is unlikely ever to be performed,<sup>20</sup> however, observational studies such as this would probably be our only source of information. It is, however, pertinent to note that our findings cannot be used to argue on a very wide basis that disability can be prevented by elective caesarean section.

Increasingly, the debate about the aetiology of perinatal brain injury emphasises the relatively small contribution of the intrapartum period. The presence of antepartum events does not mean that the intrapartum course did not contribute to the final outcome. Nevertheless, even with the best care not all potentially damaging intrapartum events are avoidable. It seems likely, however, that many babies already have encephalopathy before labour and others, whose reserve is diminished at the onset of labour, may have less capacity to cope with hypoxia when it occurs

#### Key messages

- Intrapartum risk factors for newborn encephalopathy include maternal pyrexia, persistent occipitoposterior position, and acute intrapartum events
- Operative vaginal delivery and emergency caesarean section were both associated with an increased risk whereas there was an inverse relation with elective caesarean section
- There was no evidence of intrapartum hypoxia in over 70% of cases of newborn encephalopathy
- The causes of newborn encephalopathy are heterogeneous and many relate to the antepartum period
- These findings bring into question the view that most risk factors for newborn encephalopathy lie in the intrapartum period

during labour. Elucidating these multiple pathways will be the only way we can go forward in the prevention of newborn encephalopathy.

For acknowledgements and details of contributors, funding, and competing interests please see the accompanying paper.<sup>5</sup>

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(Accepted 27 August 1998)

## Subdural haemorrhages in infants: population based study

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Editorial by Lloyd

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BMJ 1998;317:1558-61

### Abstract

**Objectives** To identify the incidence, clinical outcome, and associated factors of subdural haemorrhage in children under 2 years of age, and to determine how such cases were investigated and how many were due to child abuse.

**Design** Population based case series.

**Setting** South Wales and south west England.

**Subjects** Children under 2 years of age who had a subdural haemorrhage. We excluded neonates who developed subdural haemorrhage during their stay on a neonatal unit and infants who developed a subdural haemorrhage after infection or neurosurgical intervention.

**Main outcome measures** Incidence and clinical outcome of subdural haemorrhage in infants, the number of cases caused by child abuse, the investigations such children received, and associated risk factors.

**Results** Thirty three children (23 boys and 10 girls) were identified with subdural haemorrhage. The incidence was 12.8/100 000 children/year (95% confidence interval 5.4 to 20.2). Twenty eight cases (85%) were under 1 year of age. The incidence of subdural haemorrhage in children under 1 year of age was 21.0/100 000 children/year and was therefore higher than in the older children. The clinical outcome was poor: nine infants died and 15 had profound disability. Only 22 infants had the basic investigations of a full blood count, coagulation screen, computed tomography or magnetic resonance imaging, skeletal survey or bone scan, and

ophthalmological examination. In retrospect, 27 cases (82%) were highly suggestive of abuse.

**Conclusion** Subdural haemorrhage is common in infancy and carries a poor prognosis; three quarters of such infants die or have profound disability. Most cases are due to child abuse, but in a few the cause is unknown. Some children with subdural haemorrhage do not undergo appropriate investigations. We believe the clinical investigation of such children should include a full multidisciplinary social assessment, an ophthalmic examination, a skeletal survey supplemented with a bone scan or a skeletal survey repeated at around 10 days, a coagulation screen, and computed tomography or magnetic resonance imaging. Previous physical abuse in an infant is a significant risk factor for subdural haemorrhage and must be taken seriously by child protection agencies.

### Introduction

Subdural haemorrhage in infants and young children presents major challenges in diagnosis to doctors, social workers, and courts. It has been recognised as a form of severe child abuse as far back as 1860, but little is known about the epidemiology or prognosis of the condition.<sup>1-4</sup> In clinical practice, it is often difficult to deduce whether a subdural haematoma in an infant is caused by accident or abuse.<sup>5</sup> The shaken baby syndrome is well described both clinically and pathologically, but there are few epidemiological accounts of this condition that is associated with death and disability.<sup>6</sup>

We performed a population based case series study of children under the age of 2 years who had a

### III. 코호트 연구와 검토 사항(checklists)

#### 1. 기본 개념

코호트 연구에서 연구대상자는 장시간에 걸쳐 추적조사하며, 위험요인 또는 질병 발생 등 health outcome, 종종은 양자 모두를 지속적으로 모니터링한다. 연구 규모나 복잡성에 있어 상당한 변이가 있는데 대규모 인구집단을 수십 년간 추적조사하기도 한다. 예를 들어 the Office of Population Censuses and Surveys의 코호트 연구는 영국 인구 중 1%의 표본을 1971 인구센서스에서 파악하여 전향적으로 추적조사하고 있다. 사망이나 암 발생과 고용 상태, 주거 조건 및 이후 센서스에서 측정되는 기타 변수와의 관련성을 파악하려는 목적이다. 한편 소규모 인구집단을 수일이나 수주간 추적조사하는 경우도 있다. 유독 가스에 단기간 급성으로 노출된 소방수의 단기 영향을 보는 경우가 그 예가 될 것이다.

대부분의 코호트 연구는 알려진 또는 질병의 원인으로 의심되는 위험요인 폭로와 이후 발병 내지는 사망의 관련성을 연구한다. 단순하게는 특정 요인에 폭로된 대상자를 확인하는 동시에, 비폭로된 대조 집단을 파악한다. 이후 이 두 집단을 전향적으로 추적조사하여 각 군의 질병 발생률을 구한다. 그 발생률을 비교하여 기여위험도나 상대위험도를 추정한다. 교란변수에 대해서는 대조 집단을 폭로 집단과 짝짓기하거나, 각 군의 교란변수를 분석 단계에서 통계적으로 보정할 수 있다.

암 질환, 관상동맥 질환 또는 당뇨병 같은 만성질환 연구에 코호트 연구를 적용하는데 문제는, 대규모 인구집단을 장기간 추적조사하여야 통계적으로 의미있는 결과가 나올 정도의 발병자 수를 확보할 수 있다는 점이다. 또한 대부분의 발암 물질에서 보듯이 최초 폭로와 질병의 발현 사이에는 상당

히 긴 induction period가 필요하다.

이러한 문제를 풀기 위하여 추적조사를 후향적으로 하는 방법이 있을 수 있다. 예를 들어 관상동맥 질환이 태중 폭로 요인에 기인하였다는 가설을 규명하기 위하여, Hertfordshire군에서 1930년 이전에 출생하고 태아기와 영아기 성장에 대한 기록이 있는 사람을 선정하였다. 이들을 추적조사하여 사망한 경우 사망원인을 파악하였다. 이러한 상황에서는 출생시 체중이나 1세 때 체중과 관상동맥 사망률의 관련성을 볼 수가 있다. 물론 질병 발생을 후향적으로 정확히 파악할 수 있어야 하는데, 사망이나 암 발생 등은 일반적으로 신뢰성 있게 파악할 수 있지만, 천식 같은 질환은 어렵다. 또한 연구대상 중 폭로집단이 향후 질병 발생과 관련 있는 요인에 의하여 선정되어서도 안 된다.

또 하나의 대안으로, 대조 목적으로 대조 집단을 추적조사하는 대신에, 이미 해당 국가나 지역 인구집단에 대하여 파악된 값을 사용할 수 있다. 일반 인구집단에서 해당 위험요인에의 폭로가 무시할 만한 정도로 낮을 때에만 이러한 방법을 쓸 수 있다. 직업적인 ethylene oxide (used as a sterilant gas and in the manufacture of antifreeze) 폭로의 경우 일반 인구에서의 폭로율이 무시할 만 하므로, 국가 사망률을 비교 지표로 사용할 수 있다. 이때는 코호트에서 관찰된 사망자 수와 기대 사망자 수를 비교하게 되는데, 후자는 해당 연구 코호트의 연령, 성별, 그리고 추적조사 시기(calendar period) 하에서 일반 인구 집단과 동일한 사망률을 가정하여 계산된 숫자이다.

## 2. 검토 사항

### A. 연구의 결과가 타당하며, 비뚤림(bias)가 최소화되었는가?

#### 1. 명확하고 초점이 뚜렷한 질문을 가지고 있는가(PEO)?

- 인구집단(Population)
- 명시된 특정 기간 동안의 위험요인 폭로(Exposure)
- 결과(Outcomes)

#### 2. 코호트 연구설계가 전향적(논리적 설득력 강함)인가 후향적인가?

#### 3. 연구 개시 시점에 두 비교집단(대조집단과 폭로집단)의 관련 요인(예를 들어 성별, 연령, 사회경제적 요인, 흡연) 분포가 유사한가?

#### 4. 연구에 처음 참여한 대상자 전원이 충분히 배려되었는가?

- 추적조사율이 80%를 넘었는가? 그렇지 않다면 그 이유는 무엇인가?
- 처음 배정된 집단에 소속시켜 분석하였는가?

### B. 연구결과는 어떠한가?

#### 5. 위험요인 폭로의 영향은 어느 정도인가?

- 결과로 파악하였던 사건은 무엇이며, 측정지표는 무엇인가? (예: 상대위험도, 대응위험도, 절대위험도, 위험도 감소 내지는 증가 등)

#### 6. 폭로 효과 지표 추정치는 얼마나 정밀한가?

- 신뢰 구간 또는  $p$  값은?



C. 연구결과가 얼마나 관련(relevance) 있는가?

7. 연구 대상자가 내가 관심 있는 인구집단과 전혀 달라 본 연구결과가 아무 도움도 되지 않는가?

3. 예제 논문: cohort.pdf (총 5쪽)

Beral V, Hermon C, Kay C, Hanaford P, Darby S, Reeves G. Mortality associated with oral contraceptive use: a 25-year follow up of cohort of 46 000 women from the Royal College of General Practitioners' oral contraception study. *BMJ* 1999; **318**: 96-100.

# General practice

## Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study

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BMJ 1999;318:96-100

### Abstract

**Objective** To describe the long term effects of the use of oral contraceptives on mortality.

**Design** Cohort study with 25 year follow up. Details of oral contraceptive use and of morbidity and mortality were reported six monthly by general practitioners. 75% of the original cohort was "flagged" on the NHS central registers.

**Setting** 1400 general practices throughout Britain.

**Subjects** 46 000 women, half of whom were using oral contraceptives at recruitment in 1968-9. Median age at end of follow up was 49 years.

**Main outcome measures** Relative risks of death adjusted for age, parity, social class, and smoking.

**Results** Over the 25 year follow up 1599 deaths were reported. Over the entire period of follow up the risk of death from all causes was similar in ever users and never users of oral contraceptives (relative risk = 1.0, 95% confidence interval 0.9 to 1.1;  $P=0.7$ ) and the risk of death for most specific causes did not differ significantly in the two groups. However, among current and recent (within 10 years) users the relative risk of death from ovarian cancer was 0.2 (0.1 to 0.8;  $P=0.01$ ), from cervical cancer 2.5 (1.1 to 6.1;  $P=0.04$ ), and from cerebrovascular disease 1.9 (1.2 to 3.1,  $P=0.009$ ). By contrast, for women who had stopped use  $\geq 10$  years previously there were no significant excesses or deficits either overall or for any specific cause of death.

**Conclusion** Oral contraceptives seem to have their main effect on mortality while they are being used and in the 10 years after use ceases. Ten or more years after use ceases mortality in past users is similar to that in never users.

### Introduction

Oral contraceptives have been available for 40 years and, although their short term effects on health have been studied in detail,<sup>1,2</sup> comparatively little is known about whether these effects persist after use stops. The Royal College of General Practitioners' oral contraception study was set up in 1968 to monitor the health of women who had used oral contraceptives. We present the results of a 25 year follow up of that population

examining the effect of use of oral contraceptives on mortality in the long term.

### Subjects and methods

Over 14 months from May 1968, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were using oral contraceptives and a similar number who had never used them into the oral contraception study.<sup>1</sup> Most women (98%) were white and all were married or living as married. General practitioners were asked to provide information on oral contraceptives prescribed, pregnancies, new illness, or death for each subject every six months. During the early years of the study some general practitioners withdrew their patients and some women moved and left the study. In 1976-7 an attempt was made to "flag" the cohort on the NHS central registers in Southport and Edinburgh to provide information on death and cause of death for women who were no longer being followed regularly by their general practitioner. About 75% of the original cohort was successfully flagged, and these women have been followed for death and emigration since then. The remaining 25% could not be flagged because they or their general practitioners had left the study before the flagging procedure could be instigated and the personal details required for flagging were not available to the investigators. The mortality of the women who were followed regularly by their general practitioner was similar to that of women who left the study.<sup>3</sup>

This analysis includes deaths up to 31 December 1993. We obtained a copy of the death certificate for all women who had died, and CK or PH coded the cause of death according to ICD-8 (international classification of diseases, eighth revision),<sup>4</sup> occasionally supplementing information from the death certificate with details provided by general practitioners.<sup>5</sup> Person-years of follow up were calculated from the date of recruitment up to the date of death for the 1599 women who had died, up to the date of last contact with the general practitioner for 10 958 women who were not flagged on the NHS registers, or up to 31 December 1993 for 33 554 women who were flagged on the NHS registers and alive on that date.<sup>3</sup> For women who were no longer being followed by their general practitioner before 1 January 1977 but were

flagged no person-years were included for the period between the date of last contact with their general practitioner and 1 January 1977 because the ascertainment of deaths during that period may have been incomplete.<sup>5</sup>

Person-years were categorised by age (16-19, 20-24...70-79), parity (0, 1-2,  $\geq 3$ , not known), social class at recruitment (I-II, III, IV-V, other), and cigarette smoking at recruitment (0, 1-14/day,  $\geq 15$ /day, not known) with a standard computer program.<sup>6</sup> Person-years were further subdivided according to whether the women had taken oral contraceptives and, where appropriate, by duration of use and time since first and last use. At recruitment half (23 000) of the subjects were using oral contraceptives, but by 31 December 1993, 63% had used them at some time. Women who started using oral contraceptives after recruitment contributed person-years to the "never user" category up to the date that they began using them. For women who were flagged on the NHS registers but no longer regularly followed up by their general practitioner, we assumed that past users and never users who were over the age of 40 at the date of last contact did not subsequently take oral contraceptives. For current users and women aged under 40 at the time of last contact with their general practitioners, we assumed that use continued for two years as stated at the time of last contact, but thereafter use was classified as unknown. These assumptions about subsequent use of oral contraceptives are similar to those used in analyses of other cohort studies.<sup>7</sup>

The results presented here are based on 853 517 person-years of follow up until 31 December 1993: 517 519 in women who had used oral contraceptives and 335 998 in women who had never used them. Standardised mortality ratios were calculated by using mortality for women in England and Wales as a standard.<sup>6</sup> Relative risks were adjusted for age, parity, social class, and smoking with the Poisson regression program module of EPICURE.<sup>8</sup> P values are two tailed.

## Results

By 31 December 1993 the cohort had been followed for 25 years and the median age of the women was 49 years (48 for ever users of oral contraception and 50 for never users). During that period 1599 deaths were reported, 945 in ever users and 654 in never users (table 1). The death rate from all causes combined was 21% lower than in the UK population (overall standardised mortality ratio = 79). The relative risk of death from all causes combined after adjustment for age, parity, social class, and cigarette smoking did not differ significantly between ever users and never users (relative risk = 1.0, 95% confidence interval 0.9 to 1.1;  $P = 0.7$ ).

Table 1 also shows standardised mortality ratios and adjusted relative risks of death for common specific causes and groups of causes of death (and also for some particular causes that have been reported to be affected by oral contraceptive use) according to ever use of oral contraceptives. For most specific causes of death the standardised mortality ratios in ever users and never users of oral contraceptives were around 100 and did not differ significantly between the two groups. The few exceptions were colorectal cancer and

**Table 1** Standardised mortality ratios in ever users and never users of oral contraceptives and relative risk in ever users compared with never users

Cause of death (ICD-8 code)	Standardised mortality ratio (No of deaths)		Relative risk† (95% CI)
	Ever users	Never users	
All causes (000-999)	82 (945)	74 (654)	1.0 (0.9 to 1.1)
All cancers (140-209)	85 (474)	85 (355)	1.0 (0.8 to 1.1)
Colorectal (153-154)	62 (29)	108 (39)	0.6 (0.4 to 0.9)*
Liver (155)	126 (5)	34 (1)	5.0 (0.6 to 43.2)
Lung (162)	107 (75)	71 (40)	1.2 (0.8 to 1.8)
Breast (174)	87 (154)	81 (105)	1.1 (0.8 to 1.4)
Cervix (180)	115 (38)	57 (13)	1.7 (0.9 to 3.2)
Uterus (181-2)	22 (2)	83 (6)	0.3 (0.1 to 1.4)
Ovary (183)	49 (24)	83 (31)	0.6 (0.3 to 1.0)*
Other cancers	87 (147)	95 (120)	0.9 (0.7 to 1.1)
All circulatory diseases (390-458)	84 (237)	63 (143)	1.2 (1.0 to 1.5)
Ischaemic heart disease (410-4)	70 (98)	68 (79)	0.9 (0.7 to 1.3)
Other heart disease (420-9)	107 (19)	66 (9)	1.4 (0.6 to 3.1)
Cerebrovascular disease (430-8)	111 (87)	62 (38)	1.5 (1.0 to 2.3)*
Other circulatory	73 (33)	46 (17)	1.4 (0.8 to 2.5)
All digestive diseases (520-77)	85 (37)	74 (24)	1.1 (0.6 to 1.8)
Liver disease (570-3)	112 (23)	69 (10)	1.7 (0.8 to 3.6)
All other diseases (1-139, 210-389, 460-519, 578-799)	53 (95)	65 (89)	0.8 (0.6 to 1.0)
Violent or accidental causes (800-999)	111 (102)	68 (43)	1.6 (1.1 to 2.3)*
Suicide (950-9)	123 (39)	73 (16)	1.5 (0.8 to 2.7)

\* $P < 0.05$ . †Adjusted for age, social class, parity, and smoking.

ovarian cancer, for which the relative risks of death in users were significantly below 1.0, and cerebrovascular disease and all violent and accidental causes of death, for which the relative risks were significantly greater than 1.0. Ever use is, however, a crude measure of use of oral contraceptives.

Table 2 shows for various causes the relative risk of death compared with never users in relation to the number of years since oral contraceptives were first used. Within the first 10 years of starting use of oral contraceptives there was a significant excess mortality from all causes of death (relative risk = 1.2, 95% confidence interval 1.0 to 1.50;  $P = 0.03$ ), all circulatory diseases (2.2, 1.5 to 3.2;  $P < 0.0001$ ), and cerebrovascular disease (2.7, 1.5 to 4.9;  $P = 0.0008$ ). However, the excess mortality from these causes fell with time, this trend being significant for all circulatory disease ( $P = 0.002$ ) and cerebrovascular disease ( $P = 0.02$ ). There were 380 deaths in women who began using oral contraceptives more than 20 years before the end of follow up, and this group showed no significant excess or deficit in mortality from any specific condition or overall.

Table 3 shows the pattern of risk of death for various conditions in relation to the time since stopping use of oral contraceptives. By the end of follow up the median time since last use in the cohort was 17 years. Significant increases or decreases in risk were found mainly in current users or those who had stopped use within the past 10 years—for example, women who were current users or who stopped use in the past five years had a significantly reduced risk of ovarian cancer (0.1, 0.0 to 0.9;  $P = 0.04$ ) and a significant excess of all circulatory diseases (1.7, 1.2 to 2.4;  $P = 0.006$ ) and cerebrovascular disease (1.9, 1.1 to 3.4;  $P = 0.03$ ) and women who had stopped use five to nine years previously had a significant excess risk of cervical cancer (3.0, 1.1 to 8.1;  $P = 0.03$ ) and cerebrovascular disease (2.0, 1.1 to 3.7;  $P = 0.02$ ). Among women who had stopped use 15 or more years previously most of

**Table 2** Relative risk of death in users of oral contraceptives compared with never users according to time since first use

Cause of death (ICD-8 code)	Years since first use of oral contraceptives						(P value) test for trend by time since first use
	<10		10-19		≥20		
	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	
All causes (000-999)	1.2 (1.0 to 1.5)*	167	1.1 (0.9 to 1.2)	398	0.9 (0.8 to 1.1)	380	0.09
All cancers (140-209)	0.9 (0.7 to 1.3)	61	1.0 (0.8 to 1.2)	212	0.9 (0.8 to 1.1)	201	0.6
Colorectal (153-154)	0.7 (0.2 to 2.2)	4	0.5 (0.3 to 1.1)	11	0.6 (0.3 to 1.1)	14	0.8
Lung (162)	0.9 (0.3 to 2.3)	5	1.3 (0.8 to 2.1)	34	1.2 (0.7 to 1.9)	36	0.8
Breast (174)	1.1 (0.7 to 1.8)	22	1.2 (0.9 to 1.6)	74	1.0 (0.7 to 1.3)	58	0.8
Cervix (180)	0.8 (0.3 to 2.5)	5	2.0 (1.00 to 4.0)	22	1.8 (0.8 to 4.2)	11	0.2
Ovary (183)	0.9 (0.3 to 2.7)	4	0.5 (0.2 to 1.0)*	8	0.6 (0.3 to 1.3)	12	0.8
Other cancers	1.0 (0.6 to 1.6)	21	0.9 (0.7 to 1.2)	63	0.9 (0.7 to 1.2)	70	0.4
All circulatory diseases (390-458)	2.2 (1.5 to 3.2)**	49	1.3 (1.0 to 1.7)	99	0.9 (0.7 to 1.2)	89	0.002
Ischaemic heart disease (410-414)	1.8 (1.0 to 3.2)	14	1.0 (0.7 to 1.6)	41	0.8 (0.5 to 1.1)	43	0.02
Other heart disease (420-429)	2.1 (0.5 to 9.3)	3	1.7 (0.6 to 4.5)	8	1.1 (0.4 to 3.0)	8	0.7
Cerebrovascular disease (430-438)	2.7(1.5 to 4.9)**	23	1.7 (1.1 to 2.7)*	39	1.0 (0.6 to 1.8)	25	0.02
Other circulatory	2.4 (0.9 to 6.5)	9	1.2 (0.6 to 2.7)	11	1.2 (0.6 to 2.5)	13	0.9
All digestive diseases (520-577)	1.2 (0.5 to 3.0)	7	1.3 (0.7 to 2.4)	18	0.9 (0.4 to 1.8)	12	0.9
Liver disease (570-573)	2.0 (0.6 to 7.0)	4	1.5 (0.6 to 3.7)	9	1.8 (0.7 to 4.4)	10	0.7
All other diseases (1-139, 210-389, 460-519, 578-799)	0.9 (0.5 to 1.6)	16	0.6 (0.4 to 0.9)*	28	0.9 (0.6 to 1.3)	51	0.4
Violent and accidental causes (800-999)	1.6 (1.0 to 2.7)	34	1.5 (1.0 to 2.3)	41	1.6 (1.0 to 2.7)	27	0.9
Suicide (950-959)	1.9 (0.9 to 4.1)	16	1.4 (0.7 to 2.8)	17	1.1 (0.4 to 2.9)	6	0.2

\*P<0.05, \*\*P<0.01. †Adjusted for age, parity, social class, and smoking.

the relative risks were around 1.0. For ovarian cancer there was a weak suggestion that the protective effect associated with current or recent use wore off (test for trend, P = 0.05).

Among ever users of oral contraceptives, the average duration of use was five years. Table 4 shows the relative risk of death in relation to the duration of use of oral contraceptives. Women who used oral contraceptives for 10 or more years had a significant excess mortality from lung cancer (2.0, 1.1 to 3.5; P=0.02) and cervical cancer (4.1, 1.6 to 10.6; P=0.003). The excess deaths from lung cancer were mainly among smokers (17 deaths in smokers and three in non-smokers), the relative risk associated with 10 or more years of use of oral contraceptives being 2.0

for smokers and 2.2 for non-smokers. This excess may be a chance finding or perhaps due to residual confounding. There was also a significant trend of increasing mortality for all cancers combined and for cervical cancer in relation to duration of use (P=0.02 and 0.03, respectively).

Duration of use and time since first and last use of oral contraceptives were highly correlated, with current and recent users being more likely to have used contraceptives for longer. Table 5 shows the relative risk of death among ever users of oral contraceptives according to time since last use of oral contraceptives and duration of use. All significant results were confined to women currently using oral contraceptives or who had stopped in the past 10 years, although

**Table 3** Relative risk of death in users of oral contraceptives compared with never users according to time since last use

Cause of death (ICD-8 codes)	Years since last use of oral contraceptives								(P value) test for trend by time since last use
	Current and <5		5-9		10-14		≥15		
	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	
All causes (000-999)	1.0 (0.9 to 1.2)	199	1.1 (0.9 to 1.3)	142	1.1 (0.9 to 1.3)	189	0.9 (0.8 to 1.1)	196	1.0
All cancers (140-209)	0.9 (0.7 to 1.1)	81	1.1 (0.8 to 1.4)	79	1.1 (0.8 to 1.3)	104	0.9 (0.7 to 1.1)	99	0.9
Colorectal (153-154)	0.5 (0.2 to 1.4)	4	0.6 (0.2 to 1.6)	4	0.2 (0.1 to 0.8)*	2	1.0 (0.5 to 2.0)	12	0.1
Lung (162)	0.8 (0.3 to 1.7)	8	1.1 (0.6 to 2.2)	11	1.3 (0.8 to 2.4)	19	1.2 (0.6 to 2.1)	18	0.9
Breast (174)	1.0 (0.6 to 1.6)	28	1.5 (1.0 to 2.2)	31	1.3 (0.8 to 1.9)	33	0.9 (0.6 to 1.5)	25	0.8
Cervix (180)	2.2 (0.8 to 6.1)	9	3.0 (1.1 to 8.1)*	8	1.6 (0.5 to 4.9)	5	0.7 (0.1 to 3.2)	2	0.3
Ovary (183)	0.1 (0.0 to 0.9)*	1	0.3 (0.1 to 1.4)	2	0.7 (0.3 to 1.8)	6	0.7 (0.3 to 1.7)	6	0.05
Other cancers	1.0 (0.6 to 1.6)	31	0.9 (0.6 to 1.4)	23	1.1 (0.7 to 1.6)	39	0.8 (0.6 to 1.2)	36	0.4
All circulatory diseases (390-458)	1.7 (1.2 to 2.4)**	56	1.4 (0.9 to 2.0)	36	1.2 (0.8 to 1.7)	45	1.0 (0.7 to 1.4)	52	0.2
Ischaemic heart disease (410-414)	1.5 (0.8 to 2.8)	17	0.7 (0.3 to 1.4)	9	1.0 (0.6 to 1.6)	19	1.0 (0.6 to 1.6)	30	0.6
Other heart disease (420-429)	2.4 (0.6 to 9.7)	4	3.0 (0.9 to 10.7)	4	0.7 (0.2 to 3.4)	2	1.0 (0.3 to 3.0)	5	0.3
Cerebrovascular disease (430-438)	1.9 (1.1 to 3.4)*	26	2.0 (1.1 to 3.7)*	18	1.4 (0.8 to 2.6)	16	1.0 (0.5 to 1.9)	13	0.2
Other circulatory	1.8 (0.6 to 4.9)	9	1.7 (0.6 to 4.9)	5	1.8 (0.7 to 4.3)	8	0.1 (0.2 to 2.2)	4	0.6
All digestive diseases (520-577)	1.1 (0.4 to 2.7)	8	1.1 (0.4 to 2.9)	5	1.4 (0.6 to 3.3)	8	0.8 (0.3 to 2.1)	5	0.4
Liver disease (570-573)	1.3 (0.4 to 4.6)	4	2.0 (0.6 to 6.9)	4	1.8 (0.5 to 6.1)	4	1.7 (0.5 to 5.8)	4	0.5
All other diseases (1-139,210-389, 460-519, 578-799)	0.6 (0.3 to 1.1)	19	0.6 (0.3 to 1.1)	10	0.8 (0.5 to 1.3)	19	0.8 (0.5 to 1.3)	28	0.4
Violent and accidental causes (800-999)	1.3 (0.8 to 2.1)	35	1.3 (0.7 to 2.6)	12	1.5 (0.8 to 2.8)	13	1.5 (0.8 to 3.1)	12	0.6
Suicide (950-959)	1.4 (0.6 to 3.0)	16	1.5 (0.6 to 3.9)	6	1.2 (0.4 to 3.7)	4	1.2 (0.3 to 4.5)	3	0.7

\*P<0.05, \*\*P<0.01. †Adjusted for age, parity, social class, and smoking.

**Table 4** Relative risk of death in users of oral contraceptives compared with never users according to duration of use

Cause of death (ICD-8 code)	Duration of oral contraceptive use (years)						(P value) test for trend with duration of use
	<5		5-9		≥10		
	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	
All causes (000-999)	1.0 (0.9 to 1.1)	359	1.0 (0.9 to 1.2)	226	1.1 (0.9 to 1.3)	141	0.2
All cancers (140-209)	0.9 (0.7 to 1.1)	167	0.9 (0.7 to 1.1)	108	1.3 (1.0 to 1.6)	88	0.02
Colorectal (153-154)	0.6 (0.3 to 1.2)	11	0.8 (0.4 to 1.6)	9	0.3 (0.1 to 1.2)	2	0.6
Lung (162)	1.1 (0.6 to 1.8)	25	0.7 (0.4 to 1.4)	11	2.0 (1.1 to 3.5)*	20	0.1
Breast (174)	1.1 (0.8 to 1.6)	58	1.0 (0.7 to 1.5)	33	1.4 (0.9 to 2.1)	26	0.4
Cervix (180)	1.3 (0.5 to 3.4)	9	1.4 (0.5 to 4.0)	6	4.1 (1.6 to 10.6)**	9	0.03
Ovary (183)	0.5 (0.2 to 1.2)	8	0.6 (0.3 to 1.5)	6	0.2 (0.0 to 1.3)	1	0.5
Other cancers	0.8 (0.6 to 1.1)	56	1.0 (0.7 to 1.4)	43	1.2 (0.8 to 1.8)	30	0.1
All circulatory diseases (390-458)	1.2 (0.9 to 1.6)	95	1.3 (1.0 to 1.8)	66	1.0 (0.7 to 1.6)	28	0.6
Ischaemic heart disease (410-414)	1.0 (0.7 to 1.6)	38	1.0 (0.7 to 1.7)	25	0.8 (0.5 to 1.6)	12	0.6
Other heart disease (420-429)	1.2 (0.4 to 3.3)	7	2.1 (0.8 to 5.7)	7	0.5 (0.1 to 4.2)	1	1.0
Cerebrovascular disease (430-438)	1.5 (0.9 to 2.3)	35	1.7 (1.0 to 2.9)*	27	1.3 (0.7 to 2.6)	11	0.9
Other circulatory	1.5 (0.7 to 3.2)	15	1.2 (0.5 to 3.0)	7	1.4 (0.4 to 4.2)	4	0.8
All digestive diseases (520-577)	1.1 (0.5 to 2.2)	14	0.9 (0.4 to 2.2)	7	1.2 (0.4 to 3.3)	5	1.0
Liver disease (570-573)	1.4 (0.5 to 3.8)	7	1.4 (0.4 to 4.7)	4	3.0 (1.0 to 9.5)	5	0.3
All other diseases (1-139, 210-389, 460-519, 578-799)	0.8 (0.5 to 1.1)	41	0.8 (0.5 to 1.2)	25	0.5 (0.3 to 1.1)	10	0.6
Violent and accidental causes (800-999)	1.4 (0.9 to 2.1)	42	1.3 (0.8 to 2.3)	20	1.4 (0.7 to 2.9)	10	0.9
Suicide (950-959)	1.1 (0.5 to 2.4)	14	1.8 (0.8 to 3.9)	11	1.4 (0.5 to 4.5)	4	0.4

\*P<0.05, \*\*P<0.01. †Adjusted for age, parity, social class, and smoking.

among such women duration of use was not associated with a significant increase or decrease in mortality from any particular cause or overall. Women who stopped using oral contraceptives 10 or more years previously had no significant increases or decreases in relative risk of death from any cause, even if they had used them for 10 years or more. There were, however, only 54 deaths in this subgroup.

### Discussion

Our results suggest that most of the effects of oral contraceptives on mortality occur in current or recent

users and that few, if any, effects persist 10 years after stopping use. These results relate predominately to use of combined oral contraceptives containing 50 µg oestrogen.<sup>1</sup>

Information on use of oral contraceptives was recorded prospectively at six monthly intervals by the subjects' general practitioner and so is unlikely to be biased by subsequent events. Furthermore, because three quarters of the original cohort was "flagged" on the NHS central registers in England and Scotland and so followed routinely for death, the findings are likely to be representative of the majority of the women originally recruited. Mortality was similar in women

**Table 5** Relative risk† of death in users of oral contraceptives compared with never users according to time since last use and duration of use

Cause of death (ICD-8 code)	Current users or last use <10 years previously			Last use ≥10 years previously		
	All users (95% CI)	Duration of use <10 years (No of deaths)	Duration of use ≥10 years (No of deaths)	All users (95% CI)	Duration of use <10 years (No of deaths)	Duration of use ≥10 years (No of deaths)
All causes (000-999)	1.0 (0.9 to 1.2)	1.0 (254)	1.1 (87)	1.0 (0.9 to 1.1)	1.0 (331)	1.1 (54)
All cancers (140-209)	1.0 (0.8 to 1.2)	0.8 (104)	1.3 (56)	1.0 (0.8 to 1.2)	1.0 (171)	1.2 (32)
Colorectal (153-154)	0.5 (0.2 to 1.2)	0.5 (6)	0.5 (2)	0.6 (0.3 to 1.2)	0.7 (14)	0.0 (0)
Lung (162)	0.9 (0.5 to 1.7)	0.6 (9)	1.6 (10)	1.2 (0.8 to 2.0)	1.1 (27)	2.6 (10)
Breast (174)	1.2 (0.8 to 1.7)	1.1 (40)	1.5 (19)	1.1 (0.8 to 1.5)	1.1 (51)	1.1 (7)
Cervix (180)	2.5 (1.1 to 6.1)*	1.6 (9)	5.3 (8)	1.1 (0.4 to 3.1)	1.2 (6)	1.5 (1)
Ovary (183)	0.2 (0.1 to 0.7)*	0.2 (2)	0.3 (1)	0.7 (0.4 to 1.4)	0.8 (12)	0.0 (0)
Other cancers	0.9 (0.7 to 1.3)	0.9 (38)	1.1 (16)	0.9 (0.7 to 1.3)	0.9 (61)	1.3 (14)
All circulatory diseases(390-458)	1.5 (1.1 to 2.0)**	1.7 (76)	1.1 (16)	1.1 (0.8 to 1.4)	1.1 (85)	1.0 (12)
Ischaemic heart disease (410-414)	1.0 (0.6 to 1.7)	1.2 (21)	0.7 (5)	1.0 (0.7 to 1.5)	1.0 (42)	1.1 (7)
Other heart disease (420-429)	2.8 (0.9 to 8.4)	3.5 (7)	1.3 (1)	0.9 (0.3 to 2.4)	1.0 (7)	0.0 (0)
Cerebrovascular disease (430-438)	1.9 (1.2 to 3.1)*	2.1 (36)	1.5 (8)	1.2 (0.7 to 2.0)	1.2 (26)	1.0 (3)
Other circulatory	1.7 (0.7 to 3.9)	1.8 (12)	1.2 (2)	1.2 (0.5 to 2.7)	1.1 (10)	1.5 (2)
All digestive diseases (520-577)	1.0 (0.5 to 2.2)	0.9 (9)	1.5 (4)	1.1 (0.5 to 2.2)	1.1 (12)	0.7 (1)
Liver disease (570-573)	1.6 (0.6 to 4.4)	1.0 (4)	3.6 (4)	1.7 (0.6 to 4.7)	1.8 (7)	1.9 (1)
All other diseases (1-139, 210-389, 460-519, 578-799)	0.6 (0.4 to 1.0)*	0.7 (25)	0.4 (4)	0.8 (0.6 to 1.2)	0.8 (41)	0.8 (6)
Violent and accidental causes (800-999)	1.3 (0.8 to 2.0)	1.3 (40)	1.4 (7)	1.5 (0.9 to 2.6)	1.5 (22)	1.8 (3)
Suicide (950-959)	1.4 (0.7 to 2.9)	1.4 (19)	1.3 (3)	1.2 (0.5 to 3.1)	1.1 (6)	1.9 (1)

\*P<0.05, \*\*P<0.01. †Adjusted for age, parity, social class, and smoking. No significant differences in relative risk were found between women who used oral contraceptives for <10 and ≥10 years.

who remained under regular follow up by their general practitioner and in women who did not.<sup>3</sup> That overall mortality in our cohort was about 20% below the national average is not unexpected since women with severe chronic illnesses were not recruited.<sup>13</sup>

Death certificates were obtained for all women who died. There was good agreement between cause of death recorded on the death certificate and that reported by general practitioners.<sup>5</sup> We adjusted for the potential confounding factors of age, parity, social class, and cigarette smoking. Information on age and parity was updated throughout the follow up, whereas social class and smoking details were recorded at entry only. Information on subsequent smoking habits was obtained in 1994-5 for 11 797 members of the original cohort; re-estimation of the risk of myocardial infarction associated with oral contraceptive use based on the updated data gave virtually identical results to those based on smoking history at entry.<sup>9</sup> Use of information on smoking at entry is thus unlikely to have biased our results. We did not adjust for hypertension or other heart disease because such conditions could be in the causal pathway for death from circulatory diseases. No data on family history of these conditions or of cancer were available, but the absence of such information is unlikely to produce spurious associations suggesting that mortality varies according to the timing of oral contraceptive use.

The specific diseases showing significant excesses or deficits in mortality in our study were generally consistent with the results of other studies on the incidence of these diseases.<sup>12 10</sup> Other cohort studies have reported no significant changes in mortality among women who have ever used oral contraceptives, which might at first sight be interpreted as inconsistent with their known effects on incidence of disease.<sup>11 12</sup> What our results highlight, however, is that the effects of oral contraceptives on mortality occur mainly in current and recent users.

The effects of oral contraceptives on circulatory diseases are already recognised to be largely confined to current users, especially if they also smoke.<sup>13-16</sup> There has been concern, however, that oral contraceptive use might affect risk of cancer many years after use stops. The collaborative reanalysis of the worldwide data on the relation between breast cancer and oral contraceptive use, which included data from this study, showed that the incidence of breast cancer was slightly increased while women used oral contraceptives and in the 10 years after stopping use but that there was no excess risk 10 or more years after stopping.<sup>7</sup> Our results are consistent with this finding and suggest that other cancers of the female reproductive organs may also be affected by current and recent use of oral contraceptives but may wear off after use stops. The number of deaths from each type of cancer was small, and further data are needed to confirm our findings. Continued follow up of this and other cohorts will yield important information for the many millions of women throughout the world who have used oral contraceptives.

We thank the 1400 doctors who have contributed data to the study.

Contributors: CK set up the oral contraception study and PH took over as director in 1994. CH, SD, GR, and VB contributed to the data analysis. VB prepared the first draft of the

**Key messages**

- This 25 year follow up of 46 000 UK women found a decrease in mortality from ovarian cancer and an increase in mortality from circulatory diseases and cervical cancer among women were using oral contraceptives or had used them in the past 10 years
- 10 or more years after stopping use mortality was similar in past users and never users
- Oral contraceptives seem to have their main effect on mortality mainly while they are being used and in the 10 years after stopping use
- There is little evidence to suggest any persistent adverse effect 10 or more years after use of oral contraceptives ceases

manuscript and all other authors have contributed to it. CK is guarantor for the quality of the data; VB and CH are guarantors for the analyses and text.

Funding: Royal College of General Practitioners, British Heart Foundation, Imperial Cancer Research Fund, Medical Insurance Agency, Medical Research Council, Schering AG (Berlin), Schering Health Care (UK), Searle, and Wyeth-Ayerst International (USA).

Competing interests: None declared.

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(Accepted 15 September 1998)