Smoking during pregnancy and congenital limb deficiency

Andrew E Czeizel, Imre Kodaj, Widukind Lenz

Abstract

***Objective*—To examine genetic and environmental factors in the origin of isolated congenital limb deficiencies.**

***Design*—Case-control study with questionnaire at a family interview of cases of isolated congenital limb deficiencies (six types), negative controls (matched for age, sex, and place of residence), and positive controls (cases of sentinel anomalies).**

***Setting*—The database of the Hungarian Congenital Abnormality Registry, 1975-84, complemented by three other sources of ascertainment (1 575 904 births).**

***Subjects*—537 case-control pairs; 392 positive controls.**

***Main outcome measures*—Smoking during pregnancy, congenital limb deficiencies.**

***Results*—The adjusted rate of smoking during pregnancy was significantly higher in the mothers of cases of terminal transverse defect (relative odds 1·48; 95% confidence interval 0·98 to 2·23; P=0·017). This finding supports the hypothesis of vascular disruption as a cause of congenital limb deficiency.**

***Conclusions*—Maternal smoking during pregnancy raises the relative odds for terminal transverse limb deficiencies.**

Introduction

Maternal smoking during pregnancy causes lower birth weight and higher rates of infant mortality and spontaneous abortion.[1,2] The teratogenic effect of smoking during pregnancy, however, has not been proved unequivocally.

We studied the possible genetic and environmental factors in the origin of isolated congenital limb deficiency (one or more limbs affected without other defects) in children in Hungary with a validated diagnosis. The data were gathered over 10 years (1975-84) and totalled 1 575 904 births.

Subjects and methods

STUDY POPULATION

Cases with isolated congenital limb deficiency were selected from the Hungarian Congenital Abnormality Registry,[3] but this database was complemented by three other sources of ascertainment: records of paediatric orthopaedic surgery units (where such patients are treated), genetic counselling clinics, and the financial support services for the families of handicapped children. The database included 685 cases. Subjects with congenital limb deficiency as part of identified or unidentified congenital abnormality syndromes or associations were excluded because of their different and heterogeneous origin of deficiencies.[4]

Reported diagnoses were validated: each subject was examined and documented (description, photograph, *x* ray picture) either in our department or in their home, or detailed reports at necropsy and available medical documents were reviewed for patients who had died. Six groups of patients with isolated congenital limb deficiency were differentiated: (*a*) terminal transverse[5] (absence of the distal structures of a limb; in 96% of cases only one limb is affected); (*b*) amniogenic[6] (absence of the asymmetrical distal structure of usually more than one limb resulting from the constriction of ring shaped amniotic bands or from an early amnion rupture, or both, usually associated with syndactyly); (*c*) radial and tibial[7] (absence or severe hypoplasia of the preaxial part of the limb); (*d*) ulnar-fibular[8] (absence or severe hypoplasia of the postaxial part of the limb); (*e*) split hand or foot, or both[9] (absence of the axial ray of the limb, usually associated with syndactyly); and (*f*) intercalary[10] (absence or severe hypoplasia of the proximal part of the limb). (Morphological, demographical, and genetic data on these cases were described in our previous papers).[5-10] Misdiagnosis of congenital limb deficiency occurred in 130 cases, and we were not able to validate the diagnosis in 18 cases. These 148 cases were excluded from the analysis. Thus, the data on 537 cases with specified isolated congenital limb deficiency were analysed.

CONTROL SAMPLES

Negative control group were infants without congenital abnormalities selected from the records of the birth registry of the Hungarian Central Statistical Office and matched by sex, year of birth, and family's area of residence. Each case had three matched controls. If the first control declined to participate (12·3%) the second one was visited. If both refused (0·4%) the third was approached.

Positive control group included all cases of sentinel anomalies due to autosomal dominant inheritance from the database of the Hungarian Congenital Abnormality Registry during the study period. Each patient was examined either in our department or in his or her home as part of another project.[11] The rate of non-participation (because of untraceable address or non-compliance) was about 8%.

DATA COLLECTION

The epidemiological data on cases were obtained through mothers by the use of a self completed questionnaire at a median of 11 months after the child's birth in our department or in their home. (Cases born in 1975 were visited in 1976, whereas the data on cases born in 1976 and 1977 were obtained a few months after the birth and cases born between 1978 and 1984 were visited about one year after the birth). The questionnaire included data on lifestyle habits including maternal smoking—that is, cigarette smoking before and during pregnancy according to gestation, number of cigarettes smoked per day, and type of cigarettes. The study coordinator verified and complemented the data by using additional medical documents—for example, prenatal logbook, discharge summary—and by including information on maternal lifestyle from husbands or partners—that is, the fathers of cases—at a family interview. Data on coffee intake were not collected.

Negative controls were also visited at home by regional nurses, and the same questionnaire was completed by the mothers. Controls were studied parallel with cases born in 1975-7, and about one year later than cases born in 1978-84. Regional nurses also verified and complemented the data at the family interview.

The same questionnaire and method of data collection were used about 10-18 months (median 13) after

Department of Human Genetics and Teratology, National Institute of Hygiene—WHO Collaborating Centre for Community Control of Hereditary Diseases, Budapest, Hungary
Andrew E Czeizel, *medical geneticist*

Department of Gynaecology and Obstetrics, State Hospital, Budapest, Hungary
Imre Kodaj, *gynaecologist*

Institut für Humangenetik, Westfalische Wilhelms University, Münster, Germany
Widukind Lenz, *professor of medical genetics*

Correspondence to:
Dr Czeizel, OKI, Gyáli út 2-6, Budapest, 1966-Hungary.

BMJ 1994;308:1473-6

TABLE I—Demographic and lifestyle characteristics of parents of children with congenital limb deficiency and negative controls

Variables	Parents of:		Mothers of cases		Mothers of controls	
	Cases (n=537)	Controls (n=537)	Non-smokers (n=369)	Smokers (n=168)	Non-smokers (n=437)	Smokers (n=100)
Demographic factors:						
Mean (SD) maternal age (years)	24·7 (4·7)	25·3 (4·4)	24·9 (5·7)	24·1 (8·5)	25·5 (4·9)	24·6 (10·5)
Mean (SD) birth order	1·77 (1·01)*	1·58 (0·74)	1·73 (1·22)	1·86 (1·82)	1·55 (0·82)	1·72 (1·74)*
Mean (SD) maternal education (No of school grades)	10·4 (3·0)*	12·0 (2·8)	10·9 (3·7)	9·2 (6·0)*	12·3 (3·1)	11·0 (7·0)*
Mean (SD) paternal age (years)	27·3 (5·1)	28·2 (5·1)	27·9 (6·2)*	26·0 (9·6)*	28·4 (5·7)	27·5 (12·1)
Mean (SD) paternal education (No of school grades)	10·7 (2·7)*	12·2 (2·8)	11·2 (3·3)	9·7 (5·4)*	12·2 (3·1)	12·0 (6·5)
Lifestyle:						
No (%) of mothers who drank during pregnancy	99 (18·4)	108 (20·1)	48 (13·0)	51 (30·4)*	70 (16·0)	35 (35·0)*
No (%) who drank occasionally	92 (17·1)	104 (19·4)	46 (12·5)	46 (27·4)*	67 (15·3)	34 (34·0)*
No (%) who drank frequently	7 (1·3)	4 (0·7)	2 (0·5)	5 (3·0)	3 (0·7);	1 (1·0)

*P<0·05.

the birth of positive controls to estimate potential reporting bias of smoking during pregnancy among mothers of malformed infants.

STATISTICAL ANALYSIS

The χ^2 test was used for bivariate analysis and McNemar's test and multivariate analysis[12 13] for case-control pairs. Three categories of education ($\leq$7, 8-11, and $\geq$12 years of formal education in school) and two categories of birth order (first or second and more) were differentiated as confounders.

Results

Among demographic factors (table I) the age of the parents was not significantly different between the cases and negative controls. Birth order was higher among the cases. Parents of cases had a lower average level of education, and this was confirmed by the distribution of their types of employment. (Data on poor nutrition were not collected). Maternal alcohol consumption during pregnancy was similar in the cases and controls. Table I also shows the above variables according to whether the mothers of cases and negative controls smoked. The mothers who smoked and their partners were younger, had a higher birth order, and a lower level of education. The rate of alcohol consumption, including frequent consumption (three or more drinks a week), was also higher in mothers who smoked.

TABLE II—*Details of smoking among mothers according to group of congenital limb deficiency in children. Figures are numbers (percentages)*

Group	No of pairs	Mother never smoked	Former smoker	Smoker during pregnancy: First trimester	Smoker during pregnancy: Second and third trimesters
Terminal transverse	191	95 (49·7)	34 (17·8)	62 (32·5)	61
Matched control		119 (62·3)	34 (17·8)	38 (19·9)	27
Amniogenic	126	66 (52·4)	14 (11·1)	46 (36·5)	44
Matched control		86 (68·2)	18 (14·3)	22 (17·5)	18
Radial and tibial	40	20 (50·0)	10 (25·0)	10 (25·0)	9
Matched control		26 (65·0)	6 (15·0)	8 (20·0)	5
Ulnar-fibular	114	64 (56·1)	19 (16·7)	31 (27·2)	28
Matched control		67 (58·8)	25 (21·9)	22 (19·3)	17
Split hand and/or foot	52	27 (51·9)	7 (13·5)	18 (34·6)	18
Matched control		31 (59·6)	12 (23·1)	9 (17·3)	7
Intercalary	14	12 (85·7)	1 (7·1)	1 (7·1)	1
Matched control		12 (85·7)	1 (7·1)	1 (7·1)	1
Total	537	284 (52·9)	85 (15·8)	168 (31·3)	161
Matched control		341 (63·5)	96 (17·9)	100 (18·6)	75
Positive control*	392	241 (61·5)	68 (17·3)	83 (21·2)	63

*Sentinel anomaly present because of autosomal dominant inheritance.

Table II summarises the database of smoking before and during pregnancy. The proportion of mothers who had never smoked was lower in all groups of congenital limb deficiency except the intercalary type, whereas the proportion of former smokers—that is, women who stopped smoking before pregnancy—showed a changing pattern. Of 537 cases with validated isolated congenital limb deficiency and 537 matched negative controls, 168 mothers of cases (31·3%) and 100 mothers of matched negative controls (18·6%) smoked during the first trimester of pregnancy. Of 392 mothers of positive controls with sentinel anomalies, 83 (21·2%) smoked during pregnancy (χ^2_1=11·75; P=0·006). Only seven mothers of cases but 25 mothers of matched negative controls stopped smoking during pregnancy after the first trimester of pregnancy. Thus, the differences are more obvious in smoking during the second and third trimesters between the case and control groups. Details of maternal smoking during pregnancy and the type of cigarette showed nearly complete agreement in the replies of mothers and fathers.

The different groups with isolated congenital limb deficiency probably had different pathogenetic mechanisms and critical times during embryological development so we considered them separately. McNemar's analysis indicated a significant difference for the terminal transverse, amniogenic, and split hand and/or foot groups (table III). (Most cases with split hand and/or foot belonged to the subgroup of atypical cases with non-genetic origin.)

We also analysed any possible dose-effect relation (table IV). The bivariate analysis showed that smoking 10 or more cigarettes a day during the first trimester of pregnancy was significantly more common in the group with terminal transverse and split hand and/or foot defects. This was the case in the total groups and also between cases with amniogenic defect and their matched controls. The multivariate analysis adjusted for the educational level of mothers and birth orders, however, indicated a significantly higher rate of smoking during the first trimester of pregnancy only in the group with terminal transverse limb deficiencies.

TABLE III—*McNemar analysis of maternal smoking during pregnancy*

Congenital limb deficiency	Neither case nor control	Case—no Control—yes	Case—yes Control—no	Both case and control	Total	χ_2	P value	Relative odds (95% confidence interval)
Terminal transverse	108	21	45	17	191	8·7	0·03	2·14 (1·3 to 3·6)
Amniogenic	65	15	39	7	126	10·7	0·00	2·60 (1·4 to 4·7)
Radial and tibial	24	6	8	2	40	0·3	0·59	1·33 (0·5 to 3·8)
Ulnar-fibular	69	14	23	8	114	2·2	0·14	1·64 (0·8 to 3·2)
Split hand and/or foot	30	4	13	5	52	4·8	0·03	3·25 (1·1 to 10·0)
Intercalary	12	1	1	0	14	0·0	1·00	1·00 (0·1 to 16·0)

Discussion

Our study indicates an association between smoking during pregnancy and the occurrence of terminal transverse defect. We consider our methods to have several advantages. There was a high ascertainment of

TABLE IV—*Numbers of cigarettes smoked a day during first trimester of pregnancy and unadjusted and adjusted differences in total of cases and (negative) controls*

Congenital limb deficiency groups	1-9 cigarettes	≥10* cigarettes	Total	Unadjusted χ_1^2	Unadjusted P value	Adjusted χ_{52}^2	Adjusted P value	Relative odds (95% confidence interval)
Terminal transverse	38	24† (2)	62	7·80	0·005	87·04	0·017	148 (0·98 to 2·23)
Matched control	30	8 (1)	38					
Amniogenic	31	15 (2)	46	12·58	0·000	59·67	0·217	1·62 (1·05 to 2·52)
Matched control	14	8	22					
Radial and tibial	6	4	10	0·29	0·592	21·57	1·000	1·07 (0·61 to 1·87)
Matched control	7	1	8					
Ulnar-fibular	20	11 (2)	31	1·99	0·158	39·18	0·905	1·27 (0·80 to 2·04)
Matched control	15	7	22					
Split hand and/or foot	10	8† (1)	18	4·05	0·044	27·99	0·997	1·38 (0·79 to 2·39)
Matched control	9	0	9					
Intercalary	1	0	1	0·00	1·000	14·67	1·000	1·00 (0·52 to 1·90)
Matched control	1	0	1					
Total	106	62† (7)	168	22·99	0·000	186·40	0·000	1·68 (1·26 to 2·24)
Matched control	76	24 (1)	100					

*Number who smoked 20-29 cigarettes a day shown in brackets. One woman of child with ulnar-fibular defect smoked >30 cigarettes a day.
†$P < 0·01$.

cases in the study population; the birth prevalence of cases with congenital limb deficiency was 0·55 per 1000 total births during the study period.[14] Reported diagnoses were checked by personal examination or medical documents, or both, and only cases with validated diagnoses were included. Only cases of isolated congenital limb deficiency with more homogeneous origin were evaluated. As far as we know, this is the first case-control epidemiological study in which groups of isolated congenital limb deficiency were differentiated.

DISADVANTAGES OF STUDY

This study, however, also had the disadvantages of all retrospective studies. Firstly, selection bias may have occurred in the recruitment of cases and matched negative controls because of different compliance. Parents of cases were more likely to participate in the study regardless of age and socioeconomic status than possibly young or poorly educated parents of negative controls. This may explain why the average birth weight of negative controls (3209 g) exceeded the population average (3180 g). The multivariate analysis, however, indicated a significantly higher rate of maternal smoking during pregnancy only in one group.

Secondly, data collection bias could be caused because of some months' delay in obtaining data from negative controls in comparison with cases, because different investigators were involved (data from cases and positive controls were obtained by two social workers whereas data from negative controls were collected by several regional nurses), because the interviewers were aware of whether they interviewed a case or control parent, and because of recall bias caused by the different attitudes of parents of cases and negative controls.

Thirdly, confounding biases could be produced by some personal characteristic that differed in the parents of cases and controls—for example, socioeconomic status, poor diet, coffee intake. Women who smoke during pregnancy have different demographic characteristics.[15] Our findings confirm it. The use of adjusted odds ratios, however, may exclude this bias.

ARGUMENTS IN SUPPORT OF STUDY RESULTS

There are three arguments to support our data. In Hungary the proportion of women who smoke during pregnancy in the first trimester is about 20%,[16] which is similar to the total figure seen in negative controls (18·6%) and positive controls (21·2%) and to that for negative controls matched to cases with terminal transverse defect (19·9%). The recall of different exposures during pregnancy has been compared with exposure assessed by other methods[17,18] and almost perfect agreement was seen in the reporting of smoking behaviour before or during pregnancy.[19-21] Our main objective was to differentiate familial and sporadic cases of congenital limb deficiency and to detect possible environmental factors in their origin, but we had no hypothesis concerning the possible teratogenic effect of maternal smoking during pregnancy. We found no other possible teratogenic factors. Thus, the underreporting of smoking during pregnancy in the mothers of controls does not seem to be an important bias, and it is not reasonable to suppose an overreporting in mothers of cases.

In general, previous studies have not found an association between maternal smoking and congenital limb deficiency. To our knowledge, only Aro has reported a higher risk for the whole group of congenital limb deficiency from maternal smoking during pregnancy.[22] This weak association, however, was later explained by other covariates.[23] A tobacco related epidemic of congenital limb deficiency in pigs has been reported.[24] The role of maternal smoking during pregnancy in the origin of terminal transverse defects is theoretically plausible as maternal smoking may cause vasospasm, subsequent ischaemia, necrosis, and ultimate resorption of structures that are distal to the vascular occlusion. Among the aetiological explanations of terminal transverse defects with characteristic sporadic—that is, non-genetic—and monomelic involvement, the vascular disruption hypothesis[25,26] seems most probable.

CONCLUSION

An association between maternal smoking and one group of congenital limb deficiency obtained from a case-control epidemiological study may or may not

Clinical implications

- About one fifth of Hungarian women smoke during pregnancy
- Maternal smoking during pregnancy causes lower birth weight and a higher rate of perinatal mortality, but the teratogenic effect has not been proved
- In this case-control study six groups of cases with validated congenital limb deficiency were evaluated
- Smoking during pregnancy was 60% more common among mothers of children with terminal transverse defect
- The relative odds ratio of 1·5 reflects an important public health contribution in such a common exposure as smoking

reflect a causal relation between this putative risk factor and terminal transverse defect. It would be necessary to test this finding in a study with the measurement of cigarette related markers, such as maternal serum or urine cotinine concentrations. The low relative risk (about 1·5) for such a common exposure as smoking has important public health implications for congenital limb deficiency in the population (the attributable risk is about 14%). This risk is obviously more important than the association of congenital limb deficiency with chorionic villus sampling.[27 28] The confirmed teratogenic effect of maternal smoking may be a further strong indication for public health interventions aimed at preventing smoking during pregnancy.

We thank Márta Vitéz and István Keller for their technical help, Magda Pál for performing the multivariate analysis, and Professors J A Evans and N Wald for their comments.

1 Lowe CR. Effect of mothers' smoking habits on birth weight of their children. *BMJ* 1959;ii:673-6.
2 Kullander S, Kallen B. A prospective study of smoking and pregnancy. *Acta Obstet Gynecol Scand* 1971;50:83-94.
3 Czeizel A. The activities of the Hungarian centre for congenital anomaly control. *World Health Stat* 1988;41:219-27.
4 Evans JA, Vitéz M, Czeizel A. Congenital abnormalities associated with limb reduction deficiencies: a population study based on cases from the Hungarian congenital malformation registry, 1973-1984. *Am J Med* 1994 (in press).
5 Czeizel A, Vitéz M, Kodaj I, Lenz W. Morphology and family study on isolated unimelic terminal transverse type of congenital limb deficiency in Hungary, 1975-84. *Teratology* 1993;48:323-7.
6 Czeizel A, Vitéz M, Kodaj I, Lenz W. Study on isolated apparent amniogenic limb deficiency in Hungary, 1975-84. *Am J Med Genet* 1993;46:372-8.
7 Czeizel A, Vitéz M, Kodaj I, Lenz W. A family study on isolated congenital radial and tibial deficiencies in Hungary, 1975-84. *Clin Genet* 1993;44:32-6.
8 Czeizel A, Vitéz M, Kodaj I, Lenz W. Causal study of isolated ulnar-fibular deficiency in Hungary, 1975-84. *Am J Med Genet* 1993;46:427-33.
9 Czeizel A, Vitéz M, Kodaj I, Lenz W. An epidemiological study of isolated split hand/foot in Hungary, 1975-84. *J Med Genet* 1993;30:593-6.
10 Czeizel A, Vitéz M, Kodaj I, Lenz W. Etiological study on isolated proximal intercalary type of congenital limb deficiency in Hungary, 1975-84. *Acta Morphol Hung* 1992;40:49-65.
11 Czeizel A. Population surveillance of sentinel anomalies. *Mutat Res* 1989;212: 3-9.
12 Breslow NE, Day WE, Halvorsen KT, Prentice RL, Sabai C. Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol* 1978;108:299-307.
13 Holford TR, White C, Kelsey JL. Multivariate analysis for matched case control studies. *Am J Epidemiol* 1978;107:245-56.
14 Czeizel AE, Vitéz M, Kodaj I, Lenz W. Birth prevalence of different congenital limb deficiency types in a revised population-based Hungarian material, 1975-84. *Acta Morphol Hung* 1991;39:229-37.
15 Shiono PH, Klebanoff MA, Berendes HW: Congenital malformations and maternal smoking during pregnancy. *Teratology* 1986;34:65-71.
16 Kobor J, Petjsik B, Járai I, Pados J, Horváth M, Csébfalvy G. Effect of smoking during pregnancy on the birth weight percentile values (Hungarian). *Orv Hetil* 1988;129:21-3.
17 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.
18 Harlow SD, Linet MS. Agreement between questionnaire data and medical records. The evidence for accuracy of recall. *Am J Epidemiol* 1989;33: 159-74.
19 Olsen J, Frische G. Comparison between data obtained through questionnaires and interviews: life-style habits of pregnant women. *Scand J Soc Med* 1988;16:49-52.
20 Oakley A, Rajan L, Robertson P. A comparison of different sources of information about pregnancy and childbirth. *J Biosoc Sci* 1990;22:477-87.
21 MacKenzie SG, Lippman A. An investigation of report bias in a case-control study of pregnancy outcome. *Am J Epidemiol* 1989;129:65-75.
22 Aro T. Maternal diseases, alcohol consumption and smoking during pregnancy associated with reduction limb defects. *Early Hum Dev* 1983;9:49-57.
23 Aro T, Haapakoski J, Heinonen OP. A multivariate analysis of the risk indicators of reduction limb defects. *Int J Epidemiol* 1984;13:459-64.
24 Menges RW, Selby LA, Marienfeld CJ, Aue WA, Green DL. A tobacco related epidemic of congenital limb deformities in swine. *Environ Res* 1970;3:285-302.
25 Czeizel A. Are contraceptive pills teratogenic? *Acta Morphologia Academiae Scientiarum Hungaricae* 1980;28:177-88.
26 Hoyme EH, Jones KL, Van Allen MI, Saunders BS, Benirschke K. The vascular pathogenesis of transverse limb reduction defects. *J Pediatr* 1982;101:839-43.
27 Firth HV, Boyd PA, Chamberlain P, Mackenzie IZ, Lindenbaum RH, Huson SM. Severe limb abnormalities after chorion villus sampling at 56-66 days' gestation. *Lancet* 1991;337:762-3.
28 Mastroiacovo P, Cavalcanti DP. Limb reduction defects and chorion villus sampling. *Lancet* 1991;337:1091.

(Accepted 16 March 1994)

Randomised trial of nicotine patches in general practice: results at one year

Imperial Cancer Research Fund General Practice Research Group

Department of Public Health and Primary Care, University of Oxford, Oxford OX2 6HE
Participating members of the group are listed at the end of the article

Correspondence to:
Dr Godfrey Fowler, University Department of Public Health and Primary Care, Radcliffe Infirmary, Oxford OX2 6HE.

BMJ 1994;308:1476-7

In the largest randomised, placebo controlled trial of nicotine patches in general practice we showed that the patch was effective in helping heavy smokers (≥15 cigarettes a day) to stop smoking in the short term.[1] Among 1686 patients, rates of confirmed cessation three months after starting to use the patch were 19·4% with nicotine patches and 11·8% with placebo patches. These rates are similar to those reported by the only other randomised trial of a nicotine patch in British general practice.[2]

Trials of interventions to promote smoking cessation have shown that the effect of the intervention diminishes over time. Typically, about half of those abstinent at three months relapse by the end of a year.[3] We report here the smoking cessation rates in our trial one year after the patients began to use the patch.

Subjects, methods, and results

Selection of subjects and methods has previously been reported.[1] Briefly, 1686 patients, recruited from 19 general practices in Oxfordshire, were randomised into four equal groups: to receive a nicotine patch or a placebo patch in combination with a special booklet of support material or a standard Health Education Authority leaflet. Nicotinell TTS patches, in reducing sizes, were used over 12 weeks. Patients were reviewed by a trial nurse at one, four, eight, and 12 weeks.

At four or eight weeks, reported abstinence since the previous visit was confirmed by an exhaled carbon monoxide reading of ≤10 ppm. At 12 weeks, reported abstinence since the previous visit was confirmed by a salivary cotinine concentration ≤113·5 nmol/l (20 ng/ml).[4] For 36 patients who failed to provide a saliva sample, an exhaled carbon monoxide reading at 12 weeks of ≤10 ppm counted as confirmatiom of non-smoking.

The 263 patients with confirmed cessation at 12 weeks were reviewed by the trial nurse at 24 and 52 weeks to ascertain their smoking status. Reported smoking cessation was confirmed by salivary cotinine concentration (165 of 180 confirmed at 24 weeks; 143 of 156 confirmed at 52 weeks) or exhaled carbon monoxide. Patients who failed to attend for review were assumed to be smokers.

Two outcome measures are reported: (i) continuous cessation from 12 weeks (confirmed at 12, 24, and 52 weeks) (ii) continuous cessation from one week (confirmed at 4, 8, 12, 24, and 52 weeks). The χ^2 test was used to compare proportions. Confidence intervals were calculated with the 1991 version of the BMJ's confidence interval analysis (CIA) program.

The significant advantage of the nicotine patch over the placebo patch, seen at the end of the treatment period, was still evident (though smaller) at one year (table). Of the 163 patients given nicotine patches who were abstinent at 12 weeks, 91 (56%) maintained abstinence to 52 weeks; 76/91 (84%) were abstinent continuously from the first week.

Sustained cessation rates did not differ between patients who received the special support booklet and those who received the standard leaflet: continuous