What is already known on this topic

Few studies have examined the link between exposure to secondhand smoke and mortality

What this study adds

Adults who had never smoked and who lived with smokers had about 15% higher mortality than never smokers living in a smoke-free household

This study strengthens the case for a causal association between secondhand smoke and mortality

as smoking and exposure to secondhand smoke outside the home were more prevalent in New Zealand in the early 1980s. This may explain the apparently stronger association between household exposure and mortality in the 1996-9 cohort compared with the 1981-4 cohort.

The results from this study add to the weight of evidence of harm caused by passive smoking and support steps to reduce exposure to other people's smoke—in the home and in other settings.

We thank Jackie Fawcett and June Atkinson for technical help with data extraction and analysis.

Contributors: SEH conceived the study, analysed the data, and drafted the manuscript. TAB conceived and led the New Zealand census-mortality study (NZCMS) from which data for this study were drawn; advised on study design, data analysis, and interpretation; and contributed to the manuscript. AW and IK advised on the design, analysis, and interpretation of the study and contributed to the manuscript. SEH and TAB will act as joint guarantors for this paper.

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Competing interests: None declared.

Ethical approval: Not needed—see security statement on bmj.com

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Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial

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The overall effectiveness of nicotine replacement therapy could be greater if the therapy were targeted at those most likely to respond. Variants of the dopamine D2 receptor (*DRD2* 32806 C/T) have been implicated in the initiation and maintenance of smoking,[1 2] and these variants may also be related to response to nicotine replacement therapy.[3] Additionally, mechanisms of nicotine addiction may differ in men and women.[4] With this evidence in mind, we examined whether the response to nicotine replacement therapy is modified by sex and genotype.

Participants, methods, and results

A randomised controlled trial of nicotine patches in 1991-2 recruited 1686 heavy smokers (≥15 cigarettes a day).[5] The participants wore patches for 12 weeks. Abstinence from smoking was confirmed at one week by expired carbon monoxide concentration ≤10 ppm, and at 12, 24, and 52 weeks by salivary cotinine concentration ≤20 ng/ml (89% of cases) or by expired carbon monoxide concentration ≤10 ppm.

In 1999-2000, we contacted 1532 of the 1625 participants still alive; the mean time from trial to follow up was 8.3 years. In all, 752/1532 (49%) gave a blood sample from which *DRD2* 32806 was successfully typed. Reported abstinence at follow up was confirmed by plasma cotinine concentration ≤20 ng/ml. Throughout, non-respondents were assumed to be smoking.

Participants were older than non-participants (mean age at entry to trial, 43.0 years *v* 41.5 years; P=0.002), more likely to be female (59% (445/752) *v* 53% (410/780); P=0.01), and more likely to have quit for a year in the trial (11% (82) *v* 4% (33), P<0.0001); 744 (99%) reported their racial background as white.

The variant T allele of the dopamine D2 receptor *DRD2* 32806 (CT or TT genotype) was found in 41% (183/445) of women and 41% of men (127/307). Within each sex, there was no difference between the genotype groups in age, number of cigarettes a day, or dependency score.

We measured effectiveness of the patches by the relative odds of abstinence for active and placebo patches over five cumulative time periods: one week, 12 weeks, 24 weeks, 52 weeks, and to follow up. Treatment by genotype and sex, and their interaction, was examined in a full logistic regression model. The three way interaction by genotype by sex was significant for all time periods (P=0.009, P=0.03, P=0.006, P=0.006, P=0.004 respectively), and we therefore analysed the data for men and women separately.

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Biochemically confirmed abstinence from smoking by sex and *DRD2* 32806 genotype

Period of abstinence	Genotype	Active patch (No (%))	Placebo patch (No (%))	Odds ratio (95% confidence interval)	Difference in odds ratios (P value) Before adjustment	After adjustment*
Women						
1 week	CT or TT	42/93 (45)	13/90 (14)	4.9 (2.4 to 10.0)	0.001	0.001
	CC	33/125 (26)	34/137 (25)	1.1 (0.6 to 1.9)		
12 weeks	CT or TT	21/93 (23)	6/90 (7)	4.1 (1.6 to 10.7)	0.03	0.02
	CC	16/125 (13)	17/137 (12)	1.0 (0.5 to 2.2)		
24 weeks	CT or TT	17/93 (18)	5/90 (6)	3.8 (1.3 to 10.8)	0.03	0.02
	CC	12/125 (10)	15/137 (11)	0.9 (0.4 to 1.9)		
52 weeks	CT or TT	14/93 (15)	5/90 (6)	3.0 (1.0 to 8.7)	0.04	0.02
	CC	10/125 (8)	15/137 (11)	0.7 (0.3 to 1.6)		
8 years	CT or TT	11/93 (12)	4/90 (4)	2.9 (0.9 to 9.4)	0.02	0.01
	CC	6/125 (5)	13/137 (9)	0.5 (0.2 to 1.3)		
Men						
1 week	CT or TT	27/67 (40)	19/60 (32)	1.5 (0.7 to 3.0)	0.59	0.58
	CC	40/91 (44)	26/89 (29)	1.9 (1.0 to 3.5)		
12 weeks	CT or TT	17/67 (25)	11/60 (18)	1.5 (0.6 to 3.6)	0.46	0.43
	CC	21/91 (23)	10/89 (11)	2.4 (1.0 to 5.4)		
24 weeks	CT or TT	11/67 (16)	9/60 (15)	1.1 (0.4 to 2.9)	0.09	0.07
	CC	17/91 (19)	5/89 (6)	3.9 (1.4 to 11.0)		
52 weeks	CT or TT	9/67 (13)	9/60 (15)	0.9 (0.3 to 2.4)	0.07	0.07
	CC	15/91 (16)	5/89 (6)	3.3 (1.2 to 9.6)		
8 years	CT or TT	7/67 (10)	7/60 (12)	0.9 (0.3 to 2.7)	0.07	0.06
	CC	12/91 (13)	3/89 (3)	4.4 (1.2 to 16.0)		

Periods of abstinence are cumulative, with repeated biochemical confirmation. For details see methods.
*Adjustment for age, cigarettes per day, and dependency score before quit attempt.

In women, the effectiveness of the patches differed with genotype at all time points (table). In men, the genotype groups did not differ significantly at any time. In men with CC genotype an apparent trend in effectiveness was in an implausible direction, the patches being most effective long after therapy had stopped. In both sexes, when active and placebo groups were combined, the quit rate was not related to genotype.

Comment

In women the effectiveness of nicotine patches seems to be related to genotype. Women with the variant T allele of the dopamine D2 receptor *DRD2* 32806 showed considerable benefit from patches, whereas those with the more common CC genotype did not. The increased effectiveness reflected a tendency to a higher quit rate with the active patches and a lower quit rate with placebo patches. No significant relation between genotype and patch effectiveness was seen for men.

Modelling showed that the response bias in favour of quitters and of women could not account for our results, as the bias affected the nicotine and placebo groups equally and so cancels out in the odds ratio for patch effectiveness. The results are also not explained by an association between genotype and success at quitting, as this could account for only a marginal difference in odds ratios between genotypes and would affect men and women similarly. We therefore hypothesise that nicotine replacement therapy works through different processes and is subject to different genetic influences in men and women.

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Competing interests: None declared.

Ethical approval: Ethical approval was obtained from the Anglia and Oxford Multicentre Research Ethics Committee, and from the 86 local research ethics committees covering the areas of residence of the patients.

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Endpiece

Your time's up

Average time US patients are allowed to speak before being interrupted by their doctors: 18 seconds.

Boyle D. *The Tyranny of Numbers: Why Counting Can't Make Us Happy.* London: Flamingo, 2001

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