

# Cigarette smoking and glycaemia: the EPIC-Norfolk Study

Lincoln A Sargeant,<sup>a</sup> Kay-Tee Khaw,<sup>a</sup> Sheila Bingham,<sup>a,b</sup> Nicholas E Day,<sup>a</sup> Robert N Luben,<sup>a</sup> Suzy Oakes,<sup>a</sup> Ailsa Welch<sup>a</sup> and Nicholas J Wareham<sup>a</sup>

<b>Background</b>	Previous prospective studies have suggested that cigarette smoking may be associated with an increased risk of type 2 diabetes, but the possibility of confounding, particularly by dietary factors has not been fully examined.
<b>Methods</b>	Cross-sectional analysis of the association between cigarette smoking and HbA <sub>1C</sub> , a marker of long-term glucose homeostasis in 2704 men and 3385 women, aged 45–74 years who were recruited to a population-based study of diet and chronic disease.
<b>Results</b>	Twelve per cent of men and 11% of women reported being current smokers. Mean HbA <sub>1C</sub> was lowest in never smokers, intermediate in former smokers and highest in current smokers. There was a dose-response relationship between HbA <sub>1C</sub> levels and number of cigarettes smoked per day and a positive association with total smoking exposure as measured by pack-years. The unadjusted increase in HbA <sub>1C</sub> for 20 pack-years of smoking was 0.12% (95% CI : 0.09–0.16) in men and 0.12% (95% CI : 0.08–0.17) in women. After adjustment for possible confounders including dietary variables, the values were 0.08% (95% CI : 0.04–0.12) and 0.07% (95% CI : 0.02–0.12) for men and women, respectively. Mean HbA <sub>1C</sub> was inversely related to time since quitting smoking in men.
<b>Conclusions</b>	These results add support to the hypothesis that smoking has long-term effects on glucose homeostasis, an association that cannot be explained by confounding by dietary factors as measured in this study.
<b>Keywords</b>	Smoking, glycosylated haemoglobin, diabetes mellitus, epidemiology
<b>Accepted</b>	17 November 2000

Cigarette smoking is known to cause transient elevations in blood glucose concentration<sup>1,2</sup> and may also influence insulin sensitivity.<sup>3–6</sup> Smokers tend to have lower body mass index (BMI) than non-smokers<sup>7,8</sup> but are also more likely to have increased central adiposity.<sup>9,10</sup> Several studies have found that current smokers have higher glycosylated haemoglobin concentrations compared to non-smokers.<sup>11–14</sup>

These data suggest that smoking may be a risk factor for diabetes and prospective studies in both men<sup>15–18</sup> and women<sup>19</sup> support the association. However, other prospective studies did not find an independent association between smoking and diabetes.<sup>20–22</sup> The role of confounding by dietary factors has not been investigated. Smokers have different dietary patterns

compared to non-smokers<sup>23–25</sup> and the finding of increased risk among smokers could be due to diet rather than smoking *per se*.

Glycosylated haemoglobin (HbA<sub>1C</sub>) is a marker of long-term glucose homeostasis reflecting average blood glucose concentrations in the past 2–3 months. Microvascular complications of diabetes are associated with the concentration of HbA<sub>1C</sub><sup>26</sup> and HbA<sub>1C</sub> may predict cardiovascular disease.<sup>27</sup> Investigating the association between smoking and HbA<sub>1C</sub> may clarify the role smoking plays in the risk of diabetes and its complications.

We, therefore, examined the cross-sectional relationship between cigarette smoking and glycated haemoglobin in a large population-based study of men and women, controlling for possible confounding by dietary factors.

## Methods

### Subjects and measurements

Subjects in this study were participants of the East Anglian component of the European Prospective Investigation into Cancer (EPIC-Norfolk), a multicentre international cohort designed to

<sup>a</sup> Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK.

<sup>b</sup> MRC Dunn Human Nutrition Unit, Hills Road, Cambridge CB2 2DH, UK.

Correspondence: Dr Nick Wareham, Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK. E-mail: njw1004@medschl.cam.ac.uk

investigate the relationship between diet, cancer and chronic disease. The detailed design and operation of the study have been previously described.<sup>28,29</sup> The intention of the Norfolk EPIC study was to recruit a cohort of 25 000 men and women aged 45–74 years from the general population in a geographically circumscribed area which has relatively little outward migration in this age group. The primary objective was to create a cohort for prospective analysis. At baseline survey between 1993 and 1998, 77 630 men and women aged 45–74 years were identified from general practice age-sex registers in Norfolk and invited to participate in the study. In all, 30 447 agreed to participate and provided informed consent and 25 633 volunteers attended for a health check which included a detailed health and lifestyle questionnaire. In November 1995, midway through the recruitment of this cohort, we introduced measurement of HbA<sub>1C</sub>. The sub-cohort that has been selected for this analysis consists of all individuals who had HbA<sub>1C</sub> measurement and on whom all data had been processed by July 1998 (*n* = 6089).

Smoking history was derived from yes/no responses to the questions 'Have you ever smoked as much as one cigarette a day for as long as a year?' and 'Do you smoke cigarettes now?' Current smokers recorded the number of cigarettes smoked each day. Subjects were asked to record the age at which they started to smoke and those who stopped smoking the age at which they gave up. The number of cigarettes smoked at age 20, 30, 40, 50 years was also recorded. Pack-years of cigarette consumption were calculated from these data assuming that smoking patterns indicated at each age applied to that decade of life. A pack-year was defined as 20 cigarettes a day for a year.

Participants were also asked to record their average diet over the past year by means of a food frequency questionnaire (FFQ) that listed food items and frequency categories. Nutrient intakes were calculated by multiplying the frequency of food consumption by standard portion weights to obtain weight of food consumed per day; these were then converted to nutrient intakes using food tables.<sup>29,30</sup> Individuals who reported no alcohol consumption over the past year were considered teetotallers. Tertiles of alcohol consumption were created based on FFQ data.

Subjects were classified as vegetarians if they gave a positive response to the vegetarian option of the question 'Do you follow any particular diets?' and as supplement takers if they answered 'yes' to the question 'Have you taken any vitamins, minerals or other food supplements regularly during the past year (such as vitamin C, vitamin D, iron, calcium, fish oils, primrose oil, beta carotene, etc.)?'

The question 'Did you have any further education at college or university after you left school?' identified those who had tertiary education. Subjects were asked to choose among four options to describe the type and amount of physical activity involved in their work. These options were sedentary (most of time sitting), standing (most time standing or walking but no intense physical activity), physical work (handling heavy objects and use of tools) or heavy manual work (very vigorous physical activity). Subjects also recorded the hours spent each week on leisure-time physical activity during summer and winter.<sup>31</sup> Hormone replacement therapy (HRT) use in women was derived from yes/no responses to the questions 'Have you ever received any hormone replacement therapy?' and 'If yes, are you currently taking this treatment?'

Subjects were asked about personal illness by the question 'Has the doctor ever told you that you have any of the following?' Positive responses to the following options were used for analysis: high blood pressure (hypertension) requiring treatment with drugs, high blood cholesterol (hyperlipidaemia), angina, heart attack (myocardial infarction), stroke, other vascular disease (peripheral vascular disease), diabetes (excluding gestational diabetes) and cancer.

The group of individuals with known diabetes were defined as those who reported having been told by a doctor that they had diabetes, or by responding positively to the diabetes option of the question 'Have you modified your diet in the past year (give reasons)?' Subjects who reported diabetes in parents or siblings were classified as having a positive family history.

Following completion of the questionnaire, participants were invited to attend the general practice surgery where research nurses performed a health check. Height and weight were measured with subjects in light clothing and with their shoes removed. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 g using Salter scales. These were used to calculate the body mass index (BMI) as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Waist circumference was measured at the smallest circumference between the ribs and iliac crest to the nearest 0.1 cm and hip circumference as the maximum circumference between the iliac crest and the crotch to the nearest 0.1 cm. These measurements were used to calculate the waist-to-hip ratio (WHR).

Ninety-five per cent of the cohort provided a non-fasting blood sample. Plasma vitamin C level was measured in citrated plasma, stored overnight in a dark box at 4–7°C, and then spun at 2100 g for 15 min at 4°C. Plasma was stabilized in a standardized volume of metaphosphoric acid then stored at –70°C. Plasma vitamin C concentration was estimated using a fluorometric assay within one week of sampling.<sup>32</sup> The coefficient of variation was 5.6% at lower end of the range (mean = 33.2 µmol/l) and 4.6% at the upper end (mean = 102.3 µmol/l). HbA<sub>1C</sub> was assayed using HPLC on a Biorad Diomat.<sup>33</sup> The coefficient of variation was 3.6% at the lower end of the range (mean = 4.94%) and 3.0% at the upper end (mean = 9.76%).

### Statistical analysis

Subjects who had completed the health and lifestyle questionnaire, FFQ, health check, had given blood for HbA<sub>1C</sub> and vitamin C measurement and had complete data entry by July, 1998 formed the study population. Individuals with self-reported diabetes (*n* = 174) were excluded from analysis since they may have changed their behaviour due to the diagnosis. Subjects were classified as never smokers, former smokers or current smokers with the latter group further subdivided by the number of cigarettes smoked daily. Statistical analysis was performed using SAS Version 6.12 (SAS Institute, Cary, NC). Significance testing was done using analysis of variance (ANOVA) for means and the  $\chi^2$  test for proportions. A value of *P* < 0.05 was used for statistical significance.

### Results

The cohort defined for this analysis were the 2704 men and 3385 women subjects who had baseline HbA<sub>1C</sub> measurements and were recruited between 1995 and 1998 to the EPIC-Norfolk

study. The prevalence (n) of self-reported diabetes in men by category of smoking history was 2.2% (21) in never smokers, 4.9% (75) in former smokers, 3.3% (4) in current smokers of 1–14 cigarettes per day and 1.0% (2) in current smokers of  $\geq 15$  cigarettes per day. Corresponding figures in women were 2.0% (38), 2.5% (29), 1.0% (2) and 1.7% (3), respectively. In the subsequent analyses, we excluded these 174 participants with self-reported diabetes, since their report of diet and life-style could have been modified by the diagnostic label.

Tables 1 and 2 show characteristics by smoking status in non-diabetic men and women, respectively. Mean HbA<sub>1C</sub> among former smokers was greater than among never smokers. Among current smokers, mean HbA<sub>1C</sub> increased with smoking exposure. Smokers were generally younger and thinner compared to non-smokers. Women who were current smokers had higher mean WHR compared to non-smokers. This pattern was not seen in men where former smokers had the greatest abdominal girths. Smokers consumed more saturated fat, less fibre and less vitamin C compared to non-smokers.

The association between smoking status and HbA<sub>1C</sub> remained significant after adjustment for possible confounders. Further adjustment for dietary intake of saturated fat, fibre and vitamin C or for plasma vitamin C status did not substantially change the results (Table 3). Exclusion of individuals with doctor-diagnosed illnesses did not change the association.

Of the ever smokers, data were available for 1629 men (91%) and 1290 women (87%) for calculation of pack-years of smoking. Table 4 shows mean HbA<sub>1C</sub> by tertiles of pack-years of smoking for men and women. Mean HbA<sub>1C</sub> increased with increasing lifetime exposure to cigarette smoking. Multi-variate adjustment reduced the differences in mean HbA<sub>1C</sub> by tertiles of pack-years of smoking in both sexes but the differences remained statistically significant in men. The same pattern was found among current smokers though the mean values were not significantly different. In men, unadjusted mean (SD) HbA<sub>1C</sub> by increasing pack-year tertiles among current smokers were 5.49% (1.15), 5.48% (0.68) and 5.56% (0.59),  $P = 0.68$ . The corresponding values in women were 5.39% (0.55), 5.38% (0.64) and 5.56% (0.99),  $P = 0.15$ . In a separate analysis with pack-years considered as a continuous variable, the effect on HbA<sub>1C</sub> of a 20 pack-year increase in cigarette smoking was an increase of 0.12% (95% CI: 0.09–0.16%) in men and 0.12% (95% CI: 0.08–0.17) in women. These effects were still significant after adjustment for potential confounding factors and after exclusion of individuals who reported major illnesses.

Among former smokers, data was available on time since smoking cessation on 1187 men (81%) and 953 women (85%). Mean HbA<sub>1C</sub> decreased with increasing tertiles of years since smoking cessation in men (Table 5).

**Table 1** Characteristics of 2704 men, aged 45–74 years, of the EPIC-Norfolk cohort, 1995–1998 by smoking status (self-reported diabetes excluded)

	Never smokers (n = 918) 34.0%	Former smokers (n = 1463) 54.1%	Current smokers		P-value ( $\chi^2$ or ANOVA)
			<15 cig/day (n = 116) 4.3%	≥15 cig/day (n = 207) 7.7%	
Mean (SD)					
HbA <sub>1C</sub> (%)	5.27 (0.70)	5.38 (0.71)	5.45 (0.63)	5.56 (0.82)	0.0001
Pack-years of cigarette smoking <sup>a</sup>	0	11.5 (3–23)	18 (13–28)	30.5 (23.5–37)	
Age (years)	58.0 (8.0)	60.5 (8.4)	59.0 (8.4)	56.8 (8.0)	0.0001
BMI <sup>b</sup> (kg/m <sup>2</sup> )	26.3 (3.2)	27.0 (3.3)	26.2 (3.7)	25.7 (3.2)	0.0001
Waist circumference (cm)	95.2 (9.2)	97.5 (9.7)	95.1 (10.4)	94.4 (9.6)	0.0001
WHR <sup>c</sup>	0.926 (0.056)	0.938 (0.056)	0.931 (0.052)	0.929 (0.060)	0.0001
Total energy intake (MJ/day)	9.35 (2.59)	9.30 (2.64)	9.37 (2.48)	9.19 (2.56)	0.73
Total dietary fat (g/day)	85.1 (30.8)	83.1 (31.9)	88.0 (29.0)	88.1 (31.7)	0.85
Saturated fat (mg/day)	32.4 (13.5)	31.6 (14.0)	35.1 (13.8)	35.8 (14.6)	0.0001
Dietary fibre (mg/day)	18.8 (6.5)	18.4 (6.4)	16.6 (6.1)	15.0 (5.2)	0.0001
Dietary vitamin C (mg/day)	117.9 (55.5)	114.7 (53.5)	107.4 (55.1)	91.1 (45.3)	0.0001
Plasma vitamin C (μmol/l)	50.0 (18.3)	45.6 (18.8)	43.5 (23.3)	34.7 (22.6)	0.0001
Per cent (n)					
College or university education	48.5 (438)	36.4 (524)	31.9 (36)	36.4 (75)	0.001
Sedentary occupation	39.1 (271)	38.4 (373)	36.5 (27)	38.0 (60)	0.91 <sup>d</sup>
Lowest quintile leisure-time physical activity	24.9 (228)	23.9 (348)	25.4 (29)	34.3 (70)	0.13 <sup>d</sup>
Teetotaler	13.3 (119)	11.8 (166)	17.7 (20)	12.6 (25)	0.001 <sup>d</sup>
Any supplement use	37.2 (334)	37.7 (538)	41.4 (46)	26.7 (54)	0.016
Vegetarian	3.8 (35)	4.4 (65)	5.2 (6)	2.4 (5)	0.48
Family history of diabetes	11.7 (107)	12.6 (184)	11.2 (13)	10.1 (21)	0.73
Major illness	27.2 (250)	35.1 (513)	29.3 (34)	20.8 (43)	0.001

<sup>a</sup> Pack-years presented as median (interquartile range).

<sup>b</sup> Body mass index.

<sup>c</sup> Waist-to-hip ratio.

<sup>d</sup> P-value for all categories of variable; four categories of occupational physical activity, five quintiles of leisure time physical activity, four categories of alcohol consumption.

**Table 2** Characteristics of 3385 women, aged 45–74 years, of the EPIC-Norfolk cohort, 1995–1998 by smoking status (self-reported diabetes excluded)

	Never smokers (n = 1894) 56.0%	Former smokers (n = 1127) 33.3%	Current smokers		P-value ( $\chi^2$ or ANOVA)
			<15 cig/day (n = 191) 5.6%	≥15 cig/day (n = 173) 5.1%	
Mean (SD)					
HbA <sub>1C</sub> (%)	5.30 (0.58)	5.34 (0.74)	5.38 (0.65)	5.47 (0.74)	0.0028
Pack-years of cigarette smoking <sup>a</sup>	0	5 (1–13.5)	13 (6–18)	25 (19–30)	
Age (years)	58.9 (8.2)	59.8 (8.7)	58.0 (8.7)	55.1 (6.7)	0.0001
BMI <sup>b</sup> (kg/m <sup>2</sup> )	26.1 (4.2)	27.0 (4.7)	25.1 (4.1)	25.3 (4.1)	0.0001
Waist circumference (cm)	82.0 (10.5)	84.2 (11.1)	81.1 (10.4)	81.6 (11.0)	0.0001
WHR <sup>c</sup>	0.791 (0.061)	0.799 (0.061)	0.801 (0.060)	0.801 (0.061)	0.0021
Total energy intake (MJ/day)	8.21 (2.25)	8.08 (2.32)	7.93 (2.27)	7.79 (2.48)	0.053
Total dietary fat (g/day)	71.7 (26.8)	69.9 (27.5)	70.6 (28.3)	73.9 (30.5)	0.17
Saturated fat (mg/day)	26.8 (11.6)	26.1 (11.5)	27.8 (13.6)	29.4 (14.0)	0.006
Dietary fibre (mg/day)	19.3 (6.9)	18.9 (6.6)	17.1 (6.6)	15.2 (5.9)	0.0001
Dietary vitamin C (mg/day)	138.4 (65.6)	140.5 (64.9)	18.4 (75.4)	108.7 (53.3)	0.0001
Plasma vitamin C (μmol/l)	59.3 (19.4)	58.9 (19.9)	51.6 (21.3)	42.2 (23.9)	0.0001
Per cent (n)					
College or university education	35.0 (656)	30.5 (341)	32.6 (61)	30.2 (52)	0.062
Sedentary occupation	34.9 (430)	40.5 (271)	29.1 (37)	30.3 (37)	0.001 <sup>d</sup>
Lowest quintile leisure-time physical activity	23.0 (432)	24.0 (268)	25.8 (49)	29.4 (50)	0.037 <sup>d</sup>
Teetotaler	27.1 (500)	19.3 (208)	24.7 (45)	27.6 (45)	0.001 <sup>d</sup>
Any supplement use	55.5 (1028)	54.4 (602)	45.7 (85)	34.1 (57)	0.001
Vegetarian	7.0 (132)	5.7 (64)	3.7 (7)	6.4 (11)	0.22
Family history of diabetes	14.1 (267)	12.1 (136)	11.5 (22)	17.3 (30)	0.15
Major illness	26.5 (501)	28.9 (326)	18.9 (36)	20.2 (35)	0.006
Current HRT <sup>e</sup> use	20.4 (291)	26.0 (230)	25.5 (38)	29.1 (37)	0.001 <sup>d</sup>

<sup>a</sup> Pack-years presented as median (interquartile range).<sup>b</sup> Body mass index.<sup>c</sup> Waist-to-hip ratio.<sup>d</sup> P-value for all categories of variable; four categories of occupational physical activity, five quintiles of leisure time physical activity, four categories of alcohol consumption (teetotaler and tertiles of consumption), three categories of HRT use (never, former, current).<sup>e</sup> Hormone replacement therapy.

## Discussion

In this large population-based study, cigarette smoking was independently associated with higher HbA<sub>1C</sub> concentrations in both men and women. There was evidence of a dose-response relationship with number of cigarettes smoked in current smokers and pack-years of cigarette smoking in ever smokers. Among male former smokers there was also an inverse association between years since smoking cessation and HbA<sub>1C</sub>.

These results are consistent with those of other large epidemiological studies<sup>11,12</sup> and smaller metabolic investigations<sup>13,14</sup> that have found higher glycated haemoglobin concentrations in current smokers compared to non-smokers. However, none of these studies examined the effect of former smoking on glycated haemoglobin or whether there was a dose-dependent relationship. In addition, the role of confounding was not addressed.

Our results are unlikely to be due to chance but several potential biases need to be considered. As we have previously reported,<sup>29</sup> the EPIC-Norfolk cohort has a lower smoking prevalence than nationally representative samples.<sup>34</sup> The

proportion of men who currently smoke was 14.8%, 11.0% and 9.8% in the age groups 45–54, 55–64 and 65–74 years, respectively, compared to national figures of 28%, 25% and 20%. In women in the same age ranges, the figures for the EPIC-Norfolk cohort were 14.2%, 10.7% and 7.8% compared to 27%, 25% and 18% nationally. However, this comparison to the whole country data from the Health Survey for England 1993 may accentuate the difference in current smoking prevalence in our sample as the East Region has a relatively low smoking prevalence in this age group compared to other regions.<sup>35</sup> Even though there may be some degree of selection, bias is an unlikely explanation for our results since participants were unaware of their HbA<sub>1C</sub> status prior to the study. There is no reason to believe that smokers with high HbA<sub>1C</sub> concentrations would have differentially participated in the study. Any under- or over-reporting of smoking exposures would most likely be non-differential with respect to HbA<sub>1C</sub> status. In our analysis, we excluded individuals with self-reported diabetes who might have altered their smoking habits and lifestyle as a result of the diagnosis. It is possible that smoking exposure could have been influenced by the presence of major illnesses

**Table 3** Adjusted mean HbA<sub>1C</sub> in 2704 men and 3385 women, aged 45–74 years, of the EPIC-Norfolk cohort, 1995–1998 by smoking status (self-reported diabetes excluded)

	Never smokers	Former smokers	Current smokers		P-value (ANOVA)
			<15 cig/day	≥15 cig/day	
<b>Mean (SE)</b>					
<b>Men</b>	(n = 918)	(n = 1463)	(n = 116)	(n = 207)	
Age-adjusted	5.29 (0.02)	5.37 (0.02)	5.45 (0.07)	5.60 (0.05)	0.0001
Age and BMI <sup>a</sup>	5.29 (0.02)	5.36 (0.02)	5.45 (0.07)	5.61 (0.05)	0.0001
Age and WHR <sup>b</sup>	5.29 (0.02)	5.36 (0.02)	5.45 (0.07)	5.61 (0.05)	0.0001
Model 1	5.29 (0.02)	5.36 (0.02)	5.45 (0.07)	5.61 (0.05)	0.0001
Model 2	5.29 (0.02)	5.36 (0.02)	5.45 (0.07)	5.61 (0.05)	0.0001
Model 3	5.29 (0.02)	5.36 (0.02)	5.43 (0.07)	5.58 (0.05)	0.0001
Model 4	5.30 (0.02)	5.37 (0.02)	5.46 (0.07)	5.52 (0.05)	0.0005
<b>Women</b>	(n = 1894)	(n = 1127)	(n = 191)	(n = 173)	
Age-adjusted	5.30 (0.01)	5.32 (0.02)	5.40 (0.04)	5.56 (0.05)	0.0001
Age and BMI	5.30 (0.01)	5.31 (0.02)	5.42 (0.04)	5.57 (0.05)	0.0001
Age and WHR	5.30 (0.01)	5.32 (0.02)	5.39 (0.04)	5.54 (0.05)	0.0001
Model 1	5.31 (0.01)	5.31 (0.02)	5.41 (0.04)	5.56 (0.05)	0.0001
Model 2	5.36 (0.01)	5.37 (0.02)	5.42 (0.05)	5.59 (0.06)	0.0009
Model 3	5.37 (0.02)	5.37 (0.02)	5.41 (0.05)	5.58 (0.06)	0.007
Model 4	5.37 (0.02)	5.37 (0.02)	5.39 (0.05)	5.57 (0.06)	0.012

<sup>a</sup> Body mass index.<sup>b</sup> Waist-to-hip ratio.

Model 1: age, BMI, WHR (all continuous).

Model 2: age, BMI, WHR, family history, alcohol consumption (categorical), tertiary education, major illness, leisure-time physical activity (categorical), any supplement use, vegetarianism, (HRT in women).

Model 3: Model 2 + dietary fibre, saturated fat and dietary vitamin C (all continuous).

Model 4: Model 3 (without dietary vitamin C) + plasma vitamin C (continuous).

**Table 4** Mean HbA<sub>1C</sub> in ever smokers, aged 45–74 years, of the EPIC-Norfolk cohort, 1995–1998 by tertiles of pack-years of cigarette smoking (self-reported diabetes excluded)

	Tertile 1	Tertile 2	Tertile 3	P-value (ANOVA)
	0.5–7 pack-years	8–19 pack-years	21–123 pack-years	
<b>Mean (SD—unadjusted, SE—adjusted)</b>				
<b>Men</b>	n = 440	n = 525	n = 664	
Unadjusted	5.34 (0.72)	5.35 (0.68)	5.51 (0.77)	0.0001
Age-adjusted	5.36 (0.03)	5.35 (0.03)	5.50 (0.03)	0.0004
Adjusted for age, BMI <sup>a</sup> and WHR <sup>b</sup>	5.36 (0.03)	5.35 (0.03)	5.49 (0.03)	0.0012
Adjusted for covariates <sup>c</sup>	5.38 (0.04)	5.36 (0.03)	5.48 (0.03)	0.014
<b>Women</b>	n = 540	n = 436	n = 314	
Unadjusted	5.26 (0.62)	5.36 (0.63)	5.47 (0.78)	0.0001
Age-adjusted	5.28 (0.03)	5.36 (0.03)	5.45 (0.04)	0.0004
Adjusted for age, BMI and WHR	5.29 (0.03)	5.36 (0.03)	5.44 (0.04)	0.0037
Adjusted for covariates <sup>c</sup>	5.30 (0.03)	5.35 (0.03)	5.40 (0.04)	0.09
Adjusted for covariates <sup>c</sup> + HRT	5.37 (0.03)	5.38 (0.03)	5.46 (0.04)	0.20

<sup>a</sup> Body mass index.<sup>b</sup> Waist-to-hip ratio.<sup>c</sup> Covariates: age, BMI, WHR, family history, alcohol consumption, tertiary education, major illness, leisure-time physical activity, any supplement use, vegetarianism, dietary fibre, saturated fat and plasma vitamin C.

especially if these are smoking-related. However, the association was present when these individuals were excluded and remained significant after adjustment for major illness in multivariate models.

The possibility of confounding in this study was diminished as the association was independent of age, BMI, WHR, family history of diabetes, alcohol consumption, physical activity, tertiary education, major illness, any supplement use, vegetarianism,



**Table 5** Mean HbA<sub>1C</sub> in former smokers, aged 45–74 years, of the EPIC-Norfolk cohort, 1995–1998 by tertiles of years of smoking cessation (self-reported diabetes excluded)

	Tertile 1 1–14 years	Tertile 2 15–24 years	Tertile 3 25–59 years	P-value (ANOVA)
<b>Mean (SD—unadjusted, SE—adjusted)</b>				
<b>Men</b>	n = 397	n = 388	n = 402	
Unadjusted	5.44 (0.82)	5.35 (0.65)	5.34 (0.67)	0.11
Age-adjusted	5.46 (0.04)	5.38 (0.04)	5.30 (0.04)	0.007
Adjusted for age, BMI <sup>a</sup> and WHR <sup>b</sup>	5.45 (0.04)	5.37 (0.04)	5.31 (0.04)	0.025
Adjusted for covariates <sup>c</sup>	5.46 (0.04)	5.36 (0.04)	5.31 (0.04)	0.011
<b>Women</b>	n = 338	n = 284	n = 331	
Unadjusted	5.39 (0.88)	5.25 (0.55)	5.36 (0.67)	0.036
Age-adjusted	5.41 (0.04)	5.26 (0.04)	5.32 (0.04)	0.028
Adjusted for age, BMI and WHR	5.40 (0.04)	5.27 (0.04)	5.34 (0.04)	0.064
Adjusted for covariates <sup>c</sup>	5.35 (0.03)	5.27 (0.04)	5.31 (0.04)	0.30
Adjusted for covariates <sup>c</sup> + HRT	5.37 (0.04)	5.34 (0.04)	5.38 (0.04)	0.70

<sup>a</sup> Body mass index.<sup>b</sup> Waist-to-hip ratio.<sup>c</sup> Covariates: age, BMI, WHR, family history, alcohol consumption, tertiary education, major illness, leisure-time physical activity, any supplement use, vegetarianism, dietary fibre, saturated fat and plasma vitamin C.

dietary saturated fat, dietary fibre, dietary vitamin C, plasma vitamin C status and HRT use in women. It is possible that adjustment for factors such as BMI, the degree of central adiposity and vitamin C may be over-adjustment as these could be on the causal pathway linking cigarette smoking and hyperglycaemia. One limitation of this study is that at the time of this analysis, we did not have data on social class and used tertiary education as a proxy measure. Social class may be associated both with cigarette smoking and glycated haemoglobin as a true confounding factor. Alternatively smoking may be part of the explanation for an observed association between social class and glycated haemoglobin. The unravelling of these relationships will be an important topic for future analyses. Some of the confounding factors considered in this study, such as dietary factors and physical activity, are measured with error and, therefore, we cannot exclude residual confounding as an explanation for these results.

Despite these limitations, the results support a causal relationship between smoking and HbA<sub>1C</sub>. Although we cannot be sure of the direction of causation in cross-sectional analysis, it is reasonable to assume, given the prospective data,<sup>15–19</sup> that smoking influences HbA<sub>1C</sub> rather than vice versa. The presence of a dose-response relationship and the inverse relationship since cessation of smoking also strengthen the inference about causality. There was a 0.2–0.3% absolute or about 5% relative difference in HbA<sub>1C</sub> between smokers and non-smokers. The effect was not large but was consistent and surprising given only a single measurement of HbA<sub>1C</sub> and a truncation of the distribution of HbA<sub>1C</sub> by the exclusion of people with self-reported diabetes.

The link between cigarette smoking and abnormalities of glucose homeostasis is biologically plausible as several studies have suggested that smoking may directly impair insulin sensitivity,<sup>3–6</sup> one of the key determinants of glucose tolerance.<sup>36</sup> This observation is not consistent in all studies,<sup>13,37</sup> and at least part of the variation in findings between studies is attributable

to study design and the extent to which confounding is removed. Previous studies have shown, as we have in this study, that smoking reduces overall obesity but accentuates its central deposition.<sup>9,10,38</sup> Thus, the inconsistency of results relating smoking to measures of insulin sensitivity could be due to differences in how confounding by obesity is considered. An alternative explanation for an apparent effect of cigarette smoking on glucose tolerance would be through increased oxidative stress. This is known to be increased in cigarette smoking,<sup>39,40</sup> and experimental evidence suggests that increased oxidative stress may impair insulin action.<sup>41,42</sup>

It is also difficult from previously published data to determine whether the effect of smoking is acute or chronic. Experimental data indicate that smoking causes only transient perturbations in glucose homeostasis<sup>1,3,13</sup> but these data may underestimate the cumulative effects of cigarette smoke. The association of smoking with HbA<sub>1C</sub> suggests long-term effects that may lead to increased risk of diabetes and diabetic complications including cardiovascular disease.

## Acknowledgements

The EPIC-Norfolk study is supported by grant funding from the Cancer Research Campaign, the Medical Research Council, the Stroke Association, the British Heart Foundation, the Department of Health, the Europe Against Cancer Programme Commission of the European Union and the Ministry of Agriculture, Fisheries and Food. Dr Wareham is a MRC Clinician Scientist Fellow. We thank the staff of EPIC for their invaluable contributions and Terry Elsey and colleagues of the University of Cambridge Department of Clinical Biochemistry who performed blood assays. We are indebted to the general practitioners who allowed us to approach people on their lists and to the people of Norfolk who took part in this study.

## KEY MESSAGES

- Previous studies have suggested that smoking may be associated with an increased risk of type 2 diabetes.
- In this cross-sectional study, mean HbA<sub>1C</sub>, a marker of long-term hyperglycaemia was increased in current smokers.
- HbA<sub>1C</sub> rose by 0.12% for each 20 pack-years of smoking.
- Adjustment for confounding reduced but did not eliminate this association.
- These data add support to the hypothesis that smoking has long-term effects on glucose homeostasis.

## References

- Janzon L, Berntorp K, Hanson M, Lindell SE, Trell E. Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance test in middle-aged men. *Diabetologia* 1983;**25**:86–88.
- Sandberg H, Roman L, Zavodnick J, Kupers N. The effect of smoking on serum somatotropin, immunoreactive insulin and blood glucose levels of young adult males. *J Pharmacol Exp Ther* 1973;**184**:787–91.
- Attvall S, Fowelin J, Lager I, Von-Schenck H, Smith U. Smoking induces insulin resistance—a potential link with the insulin resistance syndrome. *J Intern Med* 1993;**233**:327–32.
- Eliasson B, Attvall S, Taskinen MR, Smith U. The insulin resistance syndrome in smokers is related to smoking habits. *Arterioscler Thromb* 1994;**14**:1946–50.
- Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet* 1992;**339**:1128–30.
- Ronnemaa T, Ronnema EM, Puukka P, Pyorala K, Laakso M. Smoking is independently associated with high plasma insulin levels in nondiabetic men. *Diabetes Care* 1996;**19**:1229–32.
- Albanes D, Jones DY, Micozzi MS, Mattson ME. Associations between smoking and body weight in the US population: analysis of NHANES II. *Am J Public Health* 1987;**77**:439–44.
- Eisen SA, Lyons MJ, Goldberg J, True WR. The impact of cigarette and alcohol consumption on weight and obesity. An analysis of 1911 monozygotic male twin pairs. *Arch Intern Med* 1993;**153**:2457–63.
- Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA* 1989;**261**:1169–73.
- Barrett-Connor E, Khaw KT. Cigarette smoking and increased central adiposity. *Ann Intern Med* 1989;**111**:783–87.
- Simon D, Senan C, Garnier P, Saint-Paul M, Papoz L. Epidemiological features of glycated haemoglobin A1c—distribution in a healthy population. The Telecom study. *Diabetologia* 1989;**32**:864–69.
- Modan M, Meytes D, Rozeman P *et al*. Significance of high HbA1 levels in normal glucose tolerance. *Diabetes Care* 1988;**11**:422–28.
- Nilsson PM, Lind L, Pollare T, Berne C, Lithell HO. Increased level of hemoglobin A1c, but not impaired insulin sensitivity, found in hypertensive and normotensive smokers. *Metabolism* 1995;**44**:557–61.
- Urborg M, Shammas R, Rajdev K. The effects of cigarette smoking on glycosylated hemoglobin in nondiabetic individuals. *J Fam Pract* 1989;**28**:529–31.
- Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J Epidemiol* 1989;**130**:1101–08.
- Uchimoto S, Tsumura K, Hayashi T *et al*. Impact of cigarette smoking on the incidence of Type 2 diabetes mellitus in middle-aged Japanese men: the Osaka Health Survey. *Diabet Med* 1999;**16**:951–55.
- Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Effects of smoking on the incidence of non-insulin-dependent diabetes mellitus. Replication and extension in a Japanese cohort of male employees. *Am J Epidemiol* 1997;**145**:103–09.
- Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 1995;**310**:555–59.
- Rimm EB, Manson JE, Stampfer MJ *et al*. Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 1993;**83**:211–14.
- Medalie JH, Papier CM, Goldbourt U, Herman JB. Major factors in the development of diabetes mellitus in 10 000 men. *Arch Intern Med* 1975;**135**:811–17.
- Wilson PW, Anderson KM, Kannel WB. Epidemiology of diabetes mellitus in the elderly: the Framingham study. *Am J Med* 1986;**80**(Suppl.5A):3–9.
- Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ* 1995;**310**:560–64.
- Walmsley CM, Bates CJ, Prentice A, Cole TJ. Relationship between cigarette smoking and nutrient intakes and blood status indices of older people living in the UK: further analysis of data from the National Diet and Nutrition Survey of people aged 65 years and over, 1994/95. *Public Health Nutr* 1999;**2**:199–208.
- Ma J, Hampl JS, Betts NM. Antioxidant intakes and smoking status: data from the continuing survey of food intakes by individuals 1994–1996. *Am J Clin Nutr* 2000;**71**:774–80.
- Cade JE, Margetts BM. Relationship between diet and smoking—is the diet of smokers different? *J Epidemiol Community Health* 1991;**45**:270–72.
- Engelgau MM, Thompson TJ, Herman WH *et al*. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. *Diabetes Care* 1997;**20**:785–91.
- Park S, Barrett CE, Wingard DL, Shan J, Edelstein S. GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes. The Rancho Bernardo Study. *Diabetes Care* 1996;**19**:450–56.
- Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;**26**(Suppl.1):S6–14.
- Day N, Oakes S, Luben R *et al*. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* 1999;**80**(Suppl.1):95–103.
- Bingham SA, Gill C, Welch A *et al*. Validation of dietary assessment methods in the UK arm of EPIC using weighed record, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol* 1997;**26**(Suppl.1):S137–51.
- Polis MA, Peeters PH, Ocke MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. *Int J Epidemiol* 1997;**26**(Suppl.1):S181–89.
- Vuilleumier JP, Keck E. Fluorometric assay of vitamin C in biological materials using a centrifugal analyser with fluorescence attachment. *J Micronutrient Anal* 1989;**5**:25–34.

- <sup>33</sup> Standing SJ, Taylor RP. Glycated haemoglobin: an assessment of high capacity liquid chromatographic and immunoassay methods. *Ann Clin Biochem* 1992;**29**:494–505.
- <sup>34</sup> Bennett N, Dodd J, Flatley J, Freet S, Boiling K. *Health Survey for England, 1993*. London: HMSO, 1995.
- <sup>35</sup> *Health Survey for England, 1996*. Available at <http://www.official-documents.co.uk/document/doh/survey96/ehtitle.htm>
- <sup>36</sup> Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;**37**:1595–607.
- <sup>37</sup> Wareham NJ, Ness EM, Byrne CD, Cox BD, Day NE, Hales CN. Cigarette smoking is not associated with hyperinsulinemia: evidence against a causal relationship between smoking and insulin resistance. *Metabolism* 1996;**45**:1551–56.
- <sup>38</sup> Slattery ML, McDonald A, Bild DE *et al.* Associations of body fat and its distribution with dietary intake, physical activity, alcohol, and smoking in blacks and whites. *Am J Clin Nutr* 1992;**55**:943–49.
- <sup>39</sup> Morrow JD, Frei B, Longmire AW *et al.* Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med* 1995;**332**:1198–203.
- <sup>40</sup> Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996;**154**:1055–60.
- <sup>41</sup> Paolisso G, D'Amore A, Volpe C *et al.* Evidence for a relationship between oxidative stress and insulin action in non-insulin-dependent (type II) diabetic patients. *Metabolism* 1994;**43**:1426–29.
- <sup>42</sup> Paolisso G, Giugliano D. Oxidative stress and insulin action: is there a relationship?. *Diabetologia* 1996;**39**:357–63.

## Commentary: Smoking and diabetes—accumulating evidence of a causal link

Ivan J Perry

Diabetes mellitus is a major public health challenge in both developed and developing countries. An estimated 135 million people worldwide had diagnosed diabetes in 1995 (of which more than 95% is Type 2), and this number is expected to rise to at least 300 million by 2025. The major part of this increase will occur in developing countries and it is estimated that by the year 2025, more than 75% of people with diabetes will reside in developing countries.<sup>1</sup> This pandemic is largely driven by the globalization of western culture and lifestyles, specifically the inter-related problems of increasing obesity<sup>2,3</sup> and decreasing physical activity levels<sup>3</sup> worldwide. Diets high in saturated fat with limited intake of fruit and vegetables are also incriminated in the development of glucose intolerance and the occurrence of Type 2 diabetes.<sup>4,5</sup>

Insulin resistance is an early and potentially modifiable metabolic defect in the pathogenesis of Type 2 diabetes. For almost a decade smoking has been linked with insulin resistance in clinical studies and with markers of insulin resistance including central obesity and dyslipidaemia.<sup>6,7</sup> Given the potential public health consequences of even a small increase in risk of a common condition such as diabetes associated with smoking, a common exposure, the possibility that smoking may play a causal role in the development of Type 2 diabetes has received surprisingly little attention. Two papers in this issue of the *Journal* addressed this hypothesis.<sup>8,9</sup> Will *et al.* present findings from a prospective

study involving over 275 000 men and 434 000 women aged  $\geq 30$  years recruited into the US Cancer Prevention study between 1959 and 1960 and followed until 1972 for incident cases of diagnosed diabetes or listing of diabetes as an underlying or contributing cause of death.<sup>8</sup> The findings from this study are consistent with a positive association between the number of cigarettes smoked per day and the incidence of diabetes mellitus in both men and women. However, in the age-adjusted data, the evidence of a dose-response relation is limited and the effect is largely confined to those smoking more than two packs of cigarettes per day. The increased risk of diabetes observed in smokers remained significant on adjustment for potential confounders including body mass index (BMI) at baseline, alcohol use, race, amount of exercise, educational level and dietary intakes of fats and carbohydrate. On quitting smoking, rates of diabetes fell gradually to that of non-smokers, providing some evidence of reversibility of the effect.

Considered in isolation, prospective studies of diabetes incidence such as that reported by Will *et al.* face potentially intractable problems of confounding and bias, particularly ascertainment bias. In these data the measures of exercise and dietary exposures were rudimentary and the adequacy of adjustment for these factors is problematical. Given the insidious onset of Type 2 diabetes and the high prevalence of undiagnosed cases in the general population, there must be concern that smokers are at increased risk of testing for diabetes given the range of common conditions associated with smoking. The argument, advanced by Will *et al.* that smokers may in fact, be less likely than non-smokers to use health services is unconvincing and it



is noteworthy that the major paper cited in support of this argument is based on a prospective study of US physicians.

This paper must, however, be set in the context of other prospective studies on the relationship between smoking and diabetes incidence. Although the majority of such studies to date have not detected a significant positive effect, most have not focused on smoking and diabetes as the major hypothesis and the majority have lacked power to detect the relatively small but important effects reported in the current study. As highlighted by Will *et al.*<sup>8</sup> it is also noteworthy that of six prospective studies with data on the number of cigarettes smoked per day, four have reported positive associations with risk of diabetes. Interestingly, the prospective data from the British Regional Heart Study is regarded as one of the negative studies in this context.<sup>3</sup> It should be noted however, that in this study of middle-aged men current smoking was associated with a 50% increased risk of diabetes relative to never smokers in analyses adjusted for age and BMI, (relative risk 1.5, 95% C.I.: 1.0–2.2). This association was attenuated on adjustment for physical activity and other potential confounders and no association with the number of cigarettes smoked was detected. However, in further analyses from this cohort, based on 17 years of follow-up and a substantially increased number of cases, the findings are broadly consistent with those from Will *et al.* (Wannamethee SG, Perry IJ, Shaper AG. *Personal communication*).

Given the problems of interpretation associated with prospective studies of incident cases of diagnosed diabetes, the data from Sargent *et al.* are illuminating.<sup>9</sup> This work is based on cross-sectional analysis of the association between cigarette smoking and haemoglobin A<sub>1C</sub> in 2704 men and 3358 women aged 45 to 74 who were recruited into the East Anglian component of the European Prospective Investigation into Cancer (EPIC-Norfolk). Participants with known diabetes were excluded from the analyses. Mean haemoglobin A<sub>1C</sub> concentrations (a marker of long-term glucose homeostasis) were lowest in never smokers, intermediate in former smokers and highest in current smokers. There was a dose-response relationship between haemoglobin A<sub>1C</sub> levels and both the number of cigarettes smoked per day and with total smoking as measured by pack-years. This association persisted in analysis adjusted for a range of potential confounders including BMI, waist-hip ratio, physical activity (based on an instrument with acceptable and well documented reliability and validity) and dietary variables, assessed using a standard food frequency questionnaire and plasma vitamin C concentration. In men mean haemoglobin A<sub>1C</sub> fell with increasing time since quitting smoking. The association between smoking and haemoglobin A<sub>1C</sub> levels persisted in analysis from which individuals reporting major illnesses were excluded. Given the focus on haemoglobin A<sub>1C</sub> as the outcome measure and the exclusion of known cases of diabetes, the findings cannot be attributed to ascertainment bias.

Given the previous data on smoking and risk of diabetes (reviewed by Will *et al.*<sup>8</sup>) and the evidence linking smoking with insulin resistance, these two papers considered together provide substantial evidence incriminating cigarette smoking as a cause of Type 2 diabetes. Concerns about residual confounding will remain. However, given that the effects of smoking on factors such as central obesity and on taste perception and diet may mediate (in part) the effect of smoking on risk of diabetes, adjustment for these variables may not be appropriate. There

is a need in observational epidemiology to focus on primary environmental, lifestyle and genetic determinants of health and disease as opposed to the minutiae of multivariate models with adjustments for confounding of uncertain appropriateness or effectiveness. Moreover, just as in nutritional epidemiology we are moving from considering the health effects of nutrients in isolation to considering the effects of foods and food groups, we should also consider the effects of inter-related lifestyle variables such as smoking, lack of exercise and dietary fat in combination.

Thus the case for smoking as a causal factor in the development of diabetes is now gathering momentum. We need further evidence on the consistency of the association in different populations, ideally from cohort studies with fasting glucose measurements at baseline and follow-up. We also need data on the reversibility of the effect given the tendency towards weight gain on quitting smoking and well-designed clinical studies of the effects of acute and chronic smoking on insulin resistance. A simple causal model is unlikely. It is probable that smoking will ultimately emerge as a causal factor in diabetes in its own right via effects on glucose homeostasis and as a marker for additional causal factors such as physical inactivity and an atherogenic diet. Although cardiovascular disease has been long investigated as a consequence of insulin resistance, it may also cause insulin resistance via effects of atheroma on the rate of glucose uptake into muscle and liver. Thus the atherogenic effects of smoking may contribute to the effect of smoking on risk of diabetes. Type 2 diabetes and cardiovascular disease are increasingly regarded as overlapping syndromes with common causal factors.<sup>3,10</sup> Smoking is now in the frame and should be presumed guilty until proven innocent.

## References

- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;**21**:1414–31.
- Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990;**132**:501–13.
- Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *Br Med J* 1995;**310**:560–64.
- Marshall JA, Hamman RF, Baxter J. High fat, low carbohydrate diet and the etiology of non-insulin dependent diabetes mellitus: The San Luis Valley Diabetes Study. *Am J Epidemiol* 1991;**134**:590–603.
- Williams DE, Wareham NJ, Cox BD, Byrne CD, Hales CN, Day NE. Frequent salad vegetable consumption is associated with a reduction in the risk of diabetes mellitus. *J Clin Epidemiol* 1999;**52**:329–35.
- Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet* 1992;**339**:1128–30.
- Barret-Connor E, Khaw K-T. Cigarette smoking and increased central adiposity. *Ann Intern Med* 1989;**111**:783–87.
- Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol* 2001;**30**:540–46.
- Sargeant LA, Khaw KT, Bingham S *et al.* Cigarette smoking and glycaemia: the EPIC-Norfolk Study. *Int J Epidemiol* 2001;**30**:547–54.
- Stern MP. Diabetes and cardiovascular disease. The “common soil” hypothesis. *Diabetes* 1995;**44**:369–74.