Cigarette smoking and risk of subsequent use of antibacterials: a follow-up of 365117 men and women

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Objectives: Antibacterial prescribing is driving antibiotic resistance. We aimed to analyse whether smoking habits are associated with susceptibility to be prescribed antibacterials in primary care and to examine whether patients’ smoking habits influence physicians’ choice of therapy.

Methods: Information on smoking habits from health surveys in 1985–99 was related to use of antibacterials 5–25 years later by linkage to the Norwegian Prescription Database. The study population included 365117 men and women, 40–45 years old. Individuals likely to have chronic obstructive airway disease were excluded. Relative risk (RR) of being dispensed antibacterials for systemic use was calculated for five levels of smoking intensity with never smokers as reference. Adjustments were made for age, education, marital status, household size, body mass index and residence (rural/urban).

Results: Fifty-six percent of the male and 69% of the female never smokers received at least one antibacterial prescription in the whole period, increasing to 68% and 82%, respectively, in heavy smokers (>19 cigarettes/day) (adjusted RR 1.17 and 1.16). The percentage receiving at least one antibacterial prescription every year was 0.5% in male and 1.9% in female never smokers, increasing to 1.1% and 4.0%, respectively, in heavy smokers (adjusted RR 2.07 and 1.89). The proportion of antibacterial users who were prescribed broad-spectrum antibacterials increased with increasing cigarette consumption.

Conclusions: Smoking habits influenced the usage of antibacterials years later with a dose–response relationship. Prescribers seem to acknowledge smoking as a risk factor for resistant bacteria since broad-spectrum antibacterials are more frequently prescribed to smokers than never smokers.

Keywords: antibiotics, epidemiology, risk factors, primary healthcare, prescriptions

Introduction

Large differences in antibacterial use are observed among countries.1 The variations may relate to differences in morbidity, differences in antibacterial resistance or cultural differences. Factors related to society (healthcare system, culture),2,3 the prescriber (therapy choice and dosage)4–7 and to patients’ attitudes and expectations8–11 have been shown to influence antibacterial prescribing. Patient-specific risk factors such as smoking, chronic obstructive pulmonary disease (COPD), fatal diseases, immunocompromising conditions, chronic organ insufficiency, obesity and alcohol abuse have been reported to increase the risk of acquiring an infection.12–15 The relationship between excessive use of antibiotics and emerging antibiotic resistance is well documented14,15 and it has been debated whether antibiotic prescribing is the correct solution for all types of infection.16–18

Cigarette smoking is associated with increased mortality.19,20 The association with infections has been explained by its negative immunological effects. Furthermore, cigarette smoking has been shown to assist microbes in causing respiratory tract infections (RTIs) by reducing local host defence, making it easier for bacteria and viruses to inhabit the lungs.21,22 Smokers with acute cough are prescribed antibiotics more frequently,23 but whether smokers are prescribed more antibacterials in general is not known.

The physician’s dilemma is to strike a balance between rapid and successful treatment of an infection, possible adverse drug effects and the need to restrict antibiotic use according to the risks for society (antibiotic resistance). Broad-spectrum antibacterials have been recommended for at-risk patients,24 but in countries where the level of antibacterial resistance is low, such as Norway, guidelines recommend narrow-spectrum antibacterials to be used as first-line treatment. Nevertheless, the physician’s prescribing decisions in clinical practice will probably...
be influenced by patient-specific risks and it is likely that the prescriber may regard smokers as being at risk of infection and of hosting resistant bacteria. Accordingly, the consequence could be higher antibacterial prescribing to smokers and probably also more frequent prescribing of broad-spectrum antibacterials, which increases the risk of developing antibacterial resistance.

We have followed a large cohort of men and women in a narrow age range. The aims of our study were to assess whether smoking habits influenced the likelihood of being prescribed antibacterials in primary care and to examine whether patients' smoking habits were associated with the prescription of broad-spectrum antibacterials.

Methods

Databases and record linkage

From 1985 until 1999, the Norwegian government conducted health surveys in all counties except for the capital, Oslo, inviting all men and women who were aged 40–42 at the time of screening to participate. The screening was continuous, but moved along counties. It lasted more than two calendar years in some counties, so the participants were 40–45 years at the time of screening. The attendance rate was generally high, but decreased over time and varied from 88% in Hedmark county in 1988 to 52% in Østfold county in 1999. The health surveys included questions about health and lifestyle.25 Data were collected using a self-administered questionnaire sent to the participants to be filled in at home. At the screening site, the questionnaire was checked for inconsistencies by a nurse, and omissions and logical inconsistencies were corrected according to a written protocol.

Data on educational and marital status, number of persons living in the same household, and type of residence (urban/rural) were obtained from the national census in 2001.

Drug use data were collected from the Norwegian Prescription Database (NorPD) for the years 2004–09. NorPD is a complete register covering the entire Norwegian population and contains information on all prescriptions dispensed in primary care in Norway. Information on drugs dispensed to hospitalized patients and patients in nursing homes is not included. The NorPD records basic demographic information on an individual level and full details of medications dispensed, with the possibility of linking all dispensed prescriptions for each person.

Data from the health surveys, the national census and NorPD were linked by the person’s unique encrypted 11-digit identification number (all individuals living in Norway are assigned such an identification number). Record linkage was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics.

Study population

A total of 392,410 individuals answered the questions on smoking habits in the health surveys. Of these, the 17,734 individuals that died before 1 January 2010 or emigrated before 1 January 2008 were excluded from the analysis (data on emigration after 1 January 2008 were not available). Furthermore, 9,559 participants assumed to have COPD were excluded, leaving 365,117 individuals for analysis. This was done to eliminate a possible mediator as cigarette smoking may cause COPD. COPD patients are highly affected by the immunological effects of smoking and prone to therapy failure.26 COPD patients were defined to be individuals who purchased p2 agonists (ATC group R03AC), anticholinergics (R03BB) or methylxanthines (R03DA) more than twice per year during the years 2008 and 2009.27

Smoking groups

The health survey questionnaire included questions about smoking (‘Have you smoked/do you smoke daily?’; ‘When did you stop smoking?’) and the participants reported the number of cigarettes smoked per day. The study population was divided into six groups with regard to daily smoking habits: never smokers; earlier smokers; and current smokers smoking 1–9, 10–14, 15–19 or >19 cigarettes/day. The group of never smokers included occasional smokers. The use of >19 cigarettes/day was defined as heavy smoking.

Other risk factors

The following risk factors were accounted for: year of birth (four 5-year groups); gender; education (four levels: <10, 10–12, 13–15 and 16+ years); residence [rural/urban (>60,000 inhabitants)]; marital status (three levels: unmarried, married/cohabiting and divorced/widowed); household size (1, 2, 3, 4, 5 and ≥6 persons); and body mass index (BMI) (<20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m²).

Antibacterial use

NorPD data were used to define the outcome variable; use of antibacterials. All medicines in Norway are classified according to the ATC system.27 Antibacterial use was defined as being dispensed prescriptions for ATC group J01 antibacterials for systemic use during 2004–09, other than methenamine (J01XX05), a drug only used for the prevention of urinary tract infections (UTIs). In 2004, the age of the participants varied from 45 years (if included in 1999) to 61 years (if included in 1985). The NorPD does not contain information on diagnoses for antimicrobials. To be able to assess antibacterial use according to indication we evaluated each antibacterial drug available in Norway by using the authority-approved indications in the Norwegian SPCs (where SPC stands for Summary of Product Characteristics) (www.legemiddelverket.no) and the National Guidelines for Antibacterial Treatment in Primary Care.28 By doing this, an estimate could be made for antibacterials purchased for the two major diagnoses leading to antibiotic prescribing in primary care—RTIs and UTIs—and the drugs were allocated to the corresponding therapy groups. The group of antibacterials mainly used for RTIs (RTI-AB) included tetracyclines (J01A), macrolides (J01FA), and penicillins [J01C excluding pivmecillinam (J01CA08)] and the group of antibacterials used for UTIs (UTI-AB) included pivmecillinam (J01CA08), trimethoprim and sulphonamides (J01E), quinolones (J01M) (in Norway; ofloxacin and ciprofloxacin) and nitrofurantoin (J01X01).

We considered two categories of antibacterial users in general and within each therapy group (RTI-AB and UTI-AB); ever users (at least one prescription of antibacterials ever during the 6 year period 2004–09) and annual users (at least one prescription each year).

To evaluate whether patients’ smoking habits influenced physicians’ therapy choice in RTIs, we calculated the proportion of users of narrow-spectrum antibacterials (defined as J01CE02 phenoxymethylpenicillin) among the users of RTI-AB. Phenoxymethylpenicillin is the first-line treatment for most RTIs in primary care.28 In 2009, this drug was the antibacterial most used in Norway; 40% of those prescribed antibacterials had phenoxymethylpenicillin prescribed.29 We elaborated on this by looking at proportions of therapy failures among never smokers and smokers. A therapy failure was defined as a new prescription of a therapy group for the same indication.27

Statistical analysis

We used Poisson regression with robust variance estimates to compute the relative risk (RR) of being prescribed antibacterials in the various smoking groups (modelled as dummy variables) with never smokers as the reference group. In addition, we computed the RR associated with an increased smoking intensity of 10 cigarettes/day as a continuous variable. Only current smokers smoking between 1 and 30
cigarettes/day were included in this analysis since the relationship between smoking intensity and antibiotic use was not well described by the Poisson regression model outside this range. The RRs were adjusted for year of birth, education, residence, marital status, household size and BMI, all modelled as dummy variables. The data were analysed in R using the vcovHC function in the sandwich package to compute robust variance estimates.

Results

Of the persons included in the analyses, 137,008 had never smoked, 87,397 were earlier smokers and 26,930, 46,314, 33,887 and 33,581 smoked 1–9, 10–14, 15–19 and >19 cigarettes/day, respectively (Table 1). Smoking was associated with a low level of education, not being married and a small household size (Table 1). The percentages of overweight persons and persons with urban residence was similar in heavy smokers and non-smokers, but smaller in moderate smokers (Table 1).

There was a dose–response relationship between smoking and antibiotic use during 2004–09 (Figure 1 and Table 2). The strength of the relationship increased with decreasing age and decreasing BMI (Figure 1 and Table S1, available as Supplementary data at JAC Online). The percentage of men being prescribed antibacterials during the whole observation period was 56.5% in never smokers, increasing to 68.0% in heavy smokers. The corresponding increase in women was from 69.1% to 81.7% (Figure 1 and Table 2). Moreover, the proportion of men that were prescribed at least one course of antibacterials every year in the 6 year period increased from 0.5% in never smokers to 1.1% in heavy smokers; the corresponding figures for women were 1.9% and 4.0% (Figure 1 and Table 3). The relationship between smoking and antibiotic use varied less with age and BMI for annual use than for ever use of antibiotics (Table S2, available as Supplementary data at JAC Online).

Heavy smokers had about a 16% higher risk of being dispensed at least one prescription of antibacterials during 2004–09 compared with never smokers after adjusting for confounders (Table 2). The risk of being dispensed antibacterials annually was roughly twice as high in heavy smokers as in never smokers (Table 3). In current smokers, an increased smoking intensity of 10 cigarettes raised the chances of at least one prescription by 6% (Table 2) and of one prescription each year by 25% for men and 31% for women, after adjusting for confounders (Tables 2 and 3).

RTI-AB was the main group of antibacterials in all smoking groups. Moreover, the proportion of users of antibacterials using RTI-AB increased according to smoking intensity, both in ever users and annual users and more so for women than for men (Figure 2; for the whole study population, see Figure S1, available as Supplementary data at JAC Online). The proportion of ever users of antibacterials that were UTI-AB ever users was less related to smoking status, while the proportion of annual antibacterial users that were annual UTI-AB users decreased with increased smoking (Figure 3). In the whole study population the proportion of UTI-AB users was less dependent on smoking status (Figure S2, available as Supplementary data at JAC Online).

The proportion of individuals being prescribed phenoxymethylpenicillin among RTI-AB users increased according to smoking group from about 60% to 65% for both men and women. However, the proportion of phenoxymethylpenicillin-only users decreased according to smoking group among RTI-AB users, from 31% to 28% in men and from 29% to 23% in women (Figure 4). Therapy failure was found in 9246 of 136,893 phenoxymethylpenicillin users, and the failure rate was slightly higher in never smokers (6.6% and 7.4% men and women, respectively) than in current smokers (6.0% and 7.0% in men and women, respectively).

Discussion

Main findings

In the present prospective population-based study we found smoking habits to influence the prescription of antibacterials years later in a dose–response manner. We have not found other longitudinal studies that have examined smoking as a risk factor for antibacterial use.

We found increased use of RTI-AB with increased smoking. RTIs are reported to be the major type of infection in primary care, and smoking has been shown to increase susceptibility to bacterial and viral RTIs. Unfortunately, information on indication is not included in the NorPD and it is therefore difficult to evaluate the appropriateness of antibacterial prescribing. However, by splitting the antibacterials into RTI-AB and UTI-AB, we were able to obtain a better picture than would be obtained by measuring only total use, and our data indicate that smoking contributes to increased antibacterial prescribing for RTIs.

We also found that former smokers used more RTI-AB than never smokers. The risk of RTIs has been found to decrease substantially after smoking cessation. A Canadian study found the risk of invasive pneumococcal disease to decrease by 14% per year after smoking cessation, returning to a non-smoker level after approximately 13 years. Such a reduction in RTIs is in line with our findings, although in our study the ex-smokers never reached the level of never smokers. However, it could be that some of those who were ex-smokers at the time of screening started smoking again later.

We found the percentage of ever users of antibacterials to be similar in earlier smokers and in current light smokers (1–9 cigarettes/day) in men, whereas in women it was lower in earlier smokers (Figure 1). This fits well with the fact that the male ex-smokers in our study reported higher cigarette consumption for a longer period than their female counterparts; on average 14 and 10 cigarettes/day in a period of 13 and 11 years, respectively (data not shown). The time from quitting to screening was also longer for female ex-smokers (10.6 years) than for male ex-smokers (9.2 years).

In Norway, the narrow-spectrum antibiotic phenoxymethylpenicillin is recommended for most RTIs as the resistance pattern for this drug is favourable. For example, Streptococcus pneumoniae is susceptible to penicillin in 97% of isolates. More current smokers in our study were prescribed phenoxymethylpenicillin than never or former smokers, indicating a higher frequency of diagnosed RTIs. Whether the higher prescribing rate for smokers is appropriate could not be shown by our data. On the other hand, the fraction of phenoxymethylpenicillin-only users among RTI-AB users decreased with increasing smoking. The most plausible interpretation of our observation is that when a physician decides to prescribe an antibacterial, broad-spectrum antibacterials are more...
Table 1. Baseline characteristics by smoking habits of the men and women included in the study

<table>
<thead>
<tr>
<th>Smoking habit</th>
<th>Individuals from health surveys, $N_1$</th>
<th>Deaths/emigrations before 2010/2008, $N_2$ (% of $N_1$)</th>
<th>Excluded due to COPD, $N_3$ (% of $N_1$)</th>
<th>Included in study, $N_4$ (% of $N_1$)</th>
<th>Mean age 2004, years (SE)</th>
<th>&gt;12 years of education, % (SE)</th>
<th>Urban residence, % (SE)</th>
<th>Married/cohabiting, % (SE)</th>
<th>Household size &gt;3 persons, % (SE)</th>
<th>BMI &gt;30, cigs, cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>never smokers</td>
<td>65043</td>
<td>2260 (3.5)</td>
<td>542 (0.9)</td>
<td>62241 (95.7)</td>
<td>52.2 (0.02)</td>
<td>41.8 (0.2)</td>
<td>19.1 (0.2)</td>
<td>75.7 (0.2)</td>
<td>52.1 (0.2)</td>
<td>9.0 (0.1)</td>
</tr>
<tr>
<td>earlier smokers</td>
<td>47148</td>
<td>1839 (3.9)</td>
<td>663 (1.5)</td>
<td>44646 (94.7)</td>
<td>52.7 (0.02)</td>
<td>29.4 (0.2)</td>
<td>19.2 (0.2)</td>
<td>78.6 (0.2)</td>
<td>45.3 (0.2)</td>
<td>10.9 (0.1)</td>
</tr>
<tr>
<td>1–9 cigs/day</td>
<td>10481</td>
<td>554 (5.3)</td>
<td>185 (1.9)</td>
<td>9742 (92.9)</td>
<td>52.2 (0.04)</td>
<td>26.2 (0.4)</td>
<td>17.6 (0.4)</td>
<td>71.8 (0.5)</td>
<td>44.2 (0.5)</td>
<td>7.4 (0.3)</td>
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<tr>
<td>10–14 cigs/day</td>
<td>20532</td>
<td>1293 (6.3)</td>
<td>484 (2.5)</td>
<td>18755 (91.3)</td>
<td>52.5 (0.03)</td>
<td>18.4 (0.3)</td>
<td>16.1 (0.3)</td>
<td>69.4 (0.3)</td>
<td>38.9 (0.4)</td>
<td>6.5 (0.2)</td>
</tr>
<tr>
<td>15–19 cigs/day</td>
<td>18970</td>
<td>1458 (7.7)</td>
<td>582 (3.3)</td>
<td>16930 (89.2)</td>
<td>52.8 (0.03)</td>
<td>17.5 (0.3)</td>
<td>17.8 (0.3)</td>
<td>68.9 (0.4)</td>
<td>34.5 (0.4)</td>
<td>7.2 (0.2)</td>
</tr>
<tr>
<td>&gt;19 cigs/day</td>
<td>24891</td>
<td>2608 (10.5)</td>
<td>1094 (4.9)</td>
<td>21189 (85.1)</td>
<td>53.1 (0.02)</td>
<td>17.9 (0.3)</td>
<td>20.2 (0.3)</td>
<td>64.6 (0.3)</td>
<td>30.3 (0.3)</td>
<td>9.7 (0.2)</td>
</tr>
<tr>
<td>total men</td>
<td>187065</td>
<td>10012 (5.4)</td>
<td>3550 (2.0)</td>
<td>173503 (92.8)</td>
<td>52.5 (0.01)</td>
<td>29.9 (0.1)</td>
<td>18.7 (0.1)</td>
<td>73.5 (0.1)</td>
<td>44.1 (0.1)</td>
<td>9.0 (0.1)</td>
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<tr>
<td><strong>Women</strong></td>
<td></td>
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<td></td>
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<tr>
<td>never smokers</td>
<td>77866</td>
<td>2176 (2.8)</td>
<td>923 (1.2)</td>
<td>74767 (96.0)</td>
<td>52.6 (0.01)</td>
<td>37.0 (0.2)</td>
<td>20.0 (0.1)</td>
<td>78.4 (0.2)</td>
<td>42.0 (0.2)</td>
<td>9.3 (0.1)</td>
</tr>
<tr>
<td>earlier smokers</td>
<td>44874</td>
<td>1304 (2.9)</td>
<td>819 (1.9)</td>
<td>42751 (95.3)</td>
<td>52.1 (0.02)</td>
<td>28.6 (0.2)</td>
<td>19.9 (0.2)</td>
<td>76.6 (0.2)</td>
<td>39.2 (0.2)</td>
<td>9.0 (0.1)</td>
</tr>
<tr>
<td>1–9 cigs/day</td>
<td>18219</td>
<td>570 (3.1)</td>
<td>461 (2.6)</td>
<td>17188 (94.3)</td>
<td>52.0 (0.03)</td>
<td>19.9 (0.3)</td>
<td>16.7 (0.3)</td>
<td>71.7 (0.3)</td>
<td>34.1 (0.4)</td>
<td>6.9 (0.2)</td>
</tr>
<tr>
<td>10–14 cigs/day</td>
<td>30153</td>
<td>1326 (4.4)</td>
<td>1268 (4.4)</td>
<td>27559 (91.4)</td>
<td>52.4 (0.02)</td>
<td>13.4 (0.2)</td>
<td>16.9 (0.2)</td>
<td>68.9 (0.3)</td>
<td>25.9 (0.3)</td>
<td>6.3 (0.1)</td>
</tr>
<tr>
<td>15–19 cigs/day</td>
<td>19268</td>
<td>1108 (5.8)</td>
<td>1203 (6.6)</td>
<td>16957 (88.0)</td>
<td>52.8 (0.03)</td>
<td>13.8 (0.3)</td>
<td>19.1 (0.3)</td>
<td>64.7 (0.4)</td>
<td>21.1 (0.3)</td>
<td>6.8 (0.2)</td>
</tr>
<tr>
<td>&gt;19 cigs/day</td>
<td>14965</td>
<td>1238 (8.3)</td>
<td>1335 (9.7)</td>
<td>12392 (82.8)</td>
<td>53.1 (0.03)</td>
<td>15.1 (0.3)</td>
<td>22.9 (0.4)</td>
<td>57.0 (0.4)</td>
<td>15.5 (0.3)</td>
<td>8.8 (0.3)</td>
</tr>
<tr>
<td>total women</td>
<td>205345</td>
<td>7722 (3.8)</td>
<td>6009 (3.0)</td>
<td>191614 (93.3)</td>
<td>52.4 (0.01)</td>
<td>26.7 (0.1)</td>
<td>19.3 (0.1)</td>
<td>73.4 (0.1)</td>
<td>34.8 (0.1)</td>
<td>8.3 (0.1)</td>
</tr>
</tbody>
</table>
often chosen for smokers than for non-smokers, possibly because physicians regard smokers as hosting resistant bacteria or other bacterial species against which phenoxymethylpenicillin has no effect. The finding that more never smokers than smokers experienced therapy failure after phenoxymethylpenicillin is difficult to explain. One explanation could be that non-smokers are more likely than smokers to have a true bacterial infection when being prescribed antibacterials; i.e. smokers may be unnecessarily over-treated. This fits with the results from a recent study that found the recovery rate for acute cough to be the same for smokers and non-smokers, although smokers were prescribed antibacterials more frequently than non-smokers. In primary care, antibacterials are often initiated empirically, and then the general risk of therapy failure is higher when using a narrow-spectrum antibacterial. However, broad-spectrum antibacterials increase the risk of antibacterial resistance. Although therapy failures are inconvenient for the affected individual, the recommendation of first-line prescription of phenoxymethylpenicillin will, in the long run, benefit society and should be continued.

Table 2. Number (percentage) of users of antibacterials (AB users) by smoking category, and RRs associated with various categories of smoking of being prescribed at least one prescription of antibacterials (ever users) in a 6 year period (2004–09); 2949 individuals with missing values for one or more confounders were excluded.

<table>
<thead>
<tr>
<th>Smoking Category</th>
<th>Males (N=172228)</th>
<th>Females (N=189940)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) AB users</td>
<td>RR \text{a}</td>
</tr>
<tr>
<td>Never smokers</td>
<td>34,869 (56.5)</td>
<td>ref</td>
</tr>
<tr>
<td>Earlier smokers</td>
<td>27,299 (61.5)</td>
<td>1.09</td>
</tr>
<tr>
<td>1–9 cigs/day</td>
<td>59,080 (61.0)</td>
<td>1.08</td>
</tr>
<tr>
<td>10–14 cigs/day</td>
<td>11,781 (63.2)</td>
<td>1.12</td>
</tr>
<tr>
<td>15–19 cigs/day</td>
<td>10,924 (64.9)</td>
<td>1.15</td>
</tr>
<tr>
<td>&gt;19 cigs/day</td>
<td>14,268 (68.0)</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>1.07c</td>
<td>1.06 (1.05–1.07)c</td>
</tr>
</tbody>
</table>

A cigs, cigarettes; CI, confidence interval; ref, reference group.
\text{a}Crude RR.
\text{b}RR adjusted for year of birth, education, marital status, household size, BMI and residence.
\text{c}RR associated with an increased smoking intensity of 10 cigarettes/day. Only current smokers smoking 30 cigarettes/day or less were included.
studies on antibiotic use. This could be explained by gynecological infections and a higher frequency of UTIs in females and also by the more frequent seeking of physicians by women than by men. It has been shown that smoking is associated with bacterial vaginosis, but an association with UTIs has not been established. In our study, the proportion of annual UTI-AB users among annual antibacterial users decreased with increased smoking, more so for women than for men (Figure 3). This finding does not imply that smoking protects against UTIs, but may be explained by a higher general intake of other antibacterials. For example, the broad-spectrum antibiotic amoxicillin is classified as being used for RTIs according to our chosen method, but it also has an effect on UTIs.

**Strengths and limitations**

The main strengths of this study are its prospective design and the large study population coming from an unselected population survey with a high response rate. The prescription data (antibacterials and drugs for COPD) were captured from a nationwide prescription database, which eliminates the

<table>
<thead>
<tr>
<th>Table 3. Number (percentage) of users of antibacterials (AB users) by smoking category, and RRs associated with various categories of smoking of being prescribed at least one prescription of antibacterials every year (annual users) in a 6 year period (2004–09); 2949 individuals with missing values for one or more confounders were excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
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<tr>
<td>Earlier smokers</td>
</tr>
<tr>
<td>1–9 cigs/day</td>
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<tr>
<td>10–14 cigs/day</td>
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<tr>
<td>15–19 cigs/day</td>
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<tr>
<td>&gt;19 cigs/day</td>
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</tbody>
</table>

<sup>a</sup>Crude RR.  
<sup>b</sup>RR adjusted for year of birth, education, marital status, household size, BMI and residence.  
<sup>c</sup>RR associated with an increased smoking intensity of 10 cigarettes/day. Only current smokers smoking 30 cigarettes/day or less were included.

Figure 2. Proportions of RTI-AB users among users of antibacterials (AB users) in the period 2004–09 by gender, age and smoking category. (a) At least one prescription (ever users); (b) at least one prescription each year (annual users). cigs, cigarettes.
problem of recall bias. Furthermore, the information on possible confounding factors was based on measured data and registries, which minimizes the risk of information and selection bias; BMI was measured at the place of screening and information on age, gender, educational and marital status, household size and place of residence were obtained from the national census in 2001.

Low social class is a well-known factor for ill health. Occupation, education and income have been used as complementary measures and proxies for social class. Not surprisingly, we found an inverse connection between education and smoking (Table 1), and also between education and the use of antibiotics (data not shown). Thus, low education is a possible confounder of the association between smoking and antibacterial use. Adjusting for education, however, did not influence the RR relating smoking to antibacterial use. Even after adjustment for several possible confounders, the RR relating smoking to the use of antibacterials was reduced only minimally.

A weakness of this study is that the data on smoking habits were not monitored during follow-up and changes in smoking habits may therefore have biased our results. To evaluate the impact of this bias we studied a small subpopulation \(n = 896\) that were screened twice, with at least 6 years between the screenings. Twenty-one percent and 12% of the male and female current smokers, respectively, at the first screening had quit at the second screening. On the other hand, only 2 of the 221 never smokers at the first screening reported current smoking at the second screening. Thus, the groups of current smokers actually contained individuals that had been ex-smokers for several years in 2004, when we started to measure antibacterial use, which means that we have probably underestimated the relationship between smoking and antibiotic use.

Deaths before the end of follow-up may also have led to underestimation of the relationship. Based on the death rates and antibacterial use in heavy smokers and non-smokers in the study population (Tables 1–3), and by estimating the association between antibacterial use and death using the death rates...
in 2008–09 and antibacterial use in 2004–07 (the death rate in users of antibacterials was roughly twice the rate in non-users for both never smokers and heavy smokers), we estimate the degree of underestimation of the RRs associated with heavy smoking in Tables 2 and 3 to be roughly 1% and 7% for ever users and annual users of antibacterials, respectively. Similarly, if antibacterial use at a given time was positively associated with later development of COPD, exclusion of COPD patients may have led to a further underestimation of the association between smoking and antibiotic use.

Other limitations that should be mentioned are that drugs used during hospitalization cannot be tracked in NorPD and that patients with other malignancies, e.g. cancer, which we used during hospitalization cannot be tracked in NorPD and between smoking and antibiotic use.

Smoking, antibacterial use and antibacterial resistance

Smoking habits increased antibacterial prescribing in a dose–response manner and physicians seem to acknowledge smoking as a risk factor since broad-spectrum antibacterials were more frequently prescribed to smokers than never smokers. Since antibacterial resistance is driven by antibacterial use, anti-smoking interventions targeting populations with high antibiotic use could be a means to fight antibiotic resistance.

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Transparency declarations
None to declare.

Supplementary data
Table S1, Table S2, Figure S1 and Figure S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org).

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