# Risk of hypersensitivity pneumonitis and interstitial lung diseases among pigeon breeders

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ABSTRACT    We studied the risk of hypersensitivity pneumonitis and other interstitial lung diseases (ILDs) among pigeon breeders.

This is a retrospective follow-up study from 1980 to 2013 of 6920 pigeon breeders identified in the records of the Danish Racing Pigeon Association. They were compared with 276 800 individually matched referents randomly drawn from the Danish population. Hospital based diagnoses of hypersensitivity pneumonitis and other ILDs were identified in the National Patient Registry 1977–2013. Stratified Cox regression analyses estimated the hazard ratios (HR) of hypersensitivity pneumonitis and other ILDs adjusted for occupation, residence and redeemed prescription of medication with ILDs as a possible side-effect. Subjects were censored at death, emigration or a diagnosis of connective tissue disease.

The overall incidence rate of ILD was 77.4 per 100 000 person-years among the pigeon breeders and 50.0 among the referents. This difference corresponded to an adjusted HR of 1.56 (95% CI 1.26–1.94). The adjusted HRs of hypersensitivity pneumonitis and other ILDs for pigeon breeders were 14.36 (95% CI 8.10–25.44) and 1.33 (95% CI 1.05–1.69), respectively.

This study shows an increased risk of ILD among pigeon breeders compared with the referent population. Protective measures are recommended even though ILD leading to hospital contact remains rare among pigeon breeders.

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## Introduction

50 years ago, Reed *et al.* [1] reported three patients with chills, fever, cough, myalgia and dyspnoea when handling pigeons. They considered these patients to be cases of acute interstitial pneumonitis of allergic origin. They named the condition pigeon breeders' lung, in keeping with the tradition of naming other forms of hypersensitivity pneumonitis, such as farmers' lung and mushroom-pickers' disease [1, 2]. During the passing years, numerous similar reports have confirmed these early observations [3–14].

Like other forms of hypersensitivity pneumonitis, pigeon breeders' lung may have acute, subacute and chronic clinical presentations [15–18]. Acute and subacute cases present flu-like symptoms concurrent with exposure to pigeons and full recovery upon cessation of exposure [19, 20]. Chronic cases occur insidiously without acute symptoms or with recurrent acute episodes superimposed on a background of chronic symptoms of dyspnoea and cough [2, 21]. Contrary to the acute and subacute forms [22], chronic hypersensitivity pneumonitis shows no or limited remission after cessation of exposure and the prognosis is poor with a 5-year survival of 71–82% [23, 24]. Hypersensitivity pneumonitis can have a distinctive histological appearance of bronchiolitis, interstitial pneumonia, granulomas and fibrotic remodelling presumably reflecting chronicity [25]. Little is known about the histopathology of acute hypersensitivity pneumonitis and the classification of hypersensitivity pneumonitis into acute, subacute and chronic forms has been challenged [25, 26]. Chronic hypersensitivity pneumonitis shares clinical features with other chronic interstitial lung diseases (ILDs) and may not be differentiated from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonitis [15, 19, 27–30].

Pigeons are kept as pets and bred for eating, racing or exhibition [23]. Exposure to antigens in pigeon droppings and bloom can initiate a type-III immune complex-mediated hypersensitivity reaction as well as activation of alveolar macrophages and T-lymphocytes. This leads to an inflammatory response and is probably the causal mechanism in hypersensitivity pneumonitis [31]. The pigeon loft can be a source of extensive exposure, depending on the number of pigeons and the type of loft [32]. Intermittent high exposure seems to favour recurrent chronic hypersensitivity pneumonitis [2, 12, 21, 33], but besides this, little is known about the exposure–response relationship.

In cross-sectional surveys of pigeon breeders, the prevalence of symptoms consistent with acute or subacute hypersensitivity pneumonitis is reported to vary between 0 and 44% [3–14]. In hypersensitivity pneumonitis patient series, pigeons or other birds have been identified as the causative exposure in 34–81% of cases [25, 34, 35]. To our knowledge, the incidence of hypersensitivity pneumonitis and other ILDs among subjects exposed to pigeons is not known. The objective of this study is to analyse the incidence of hypersensitivity pneumonitis, and other ILDs among pigeon breeders, and compare it to that of a comparable, but unexposed population.

## Methods and materials

### Population

From the Danish Racing Pigeon Association, we obtained all available records of pigeon breeding members (1957–2014) with information on name, address, date of birth and earliest year of recorded membership. For those first enrolled in 2001 or later, we also obtained information on date of enrolment and possible resignation.

A data set of 9712 records with an unknown number of duplicates was generated after all institutional members or members residing outside Denmark were excluded. From name and birthday, the 10-digit personal identification number, which all residents have been assigned at birth or upon later residence in Denmark since 1968, were identified by Statistics Denmark from a national database of all citizens. 7577 subjects with a unique match for name and date of birth were identified.

For each of these we defined start of follow-up as January 1, 1980, since this was the first year with valid data on residence, or the earliest year of a recorded membership in the Danish Racing Pigeon Association if later. The pigeon breeder was required to be alive, resident in Denmark and have no prior diagnosis of ILD or connective tissue disease at start of follow-up. A total of 6920 pigeon breeders met these criteria, and were included in the current study. A reference group of 40 subjects per pigeon breeder, with the same sex and year of birth and fulfilling the same requirements as the pigeon breeders at start of follow-up, was randomly sampled from the general population in Denmark. As referents were randomly sampled, it was possible for an individual to be sampled more than once, which was the case for 15 478 (12%) referents.

The identity of the subjects constituting the final study population was unknown to us and no contact was made with the individual participants. The Danish Data Protection Agency approved the study (2014-41-3367). In Denmark, registry studies do not need to be approved by the Danish Health Research Ethics Committee system.

A total of 807 pigeon breeders were enrolled for the first time in the Danish Racing Pigeon Association in 2001 or later. For these members we had access to information on the date of enrolment, and thus a complete history of their pigeon breeding. They constituted the inception population together with their 32 280 matched referents.

### Hypersensitivity pneumonitis and other ILDs

We identified all diagnoses for all patients treated at public hospitals (inpatients 1977–2013 and outpatients 1994–2013) and private hospitals (inpatients and outpatients 2003–2013) by record linkage with the Danish National Patient Register, which also contained information of the dates on which a diagnosis was given. Diagnoses were coded according to the International Classification of Diseases (ICD) 8th (1977–1993) and 10th (1994–2013) revisions. We defined hypersensitivity pneumonitis in ICD-8 as 516.1 and in ICD-10 as J66 and J67. Other ILDs were defined according to ICD-8 as 515, 516.0, 516.2, 517 and 519.2 and in ICD-10 as J60-J65, J68, J70, J80, J82 and J84. If a diagnosis of hypersensitivity pneumonitis was given on the same date as a diagnosis of other ILD, hypersensitivity pneumonitis was prioritised.

### Censoring

Information on date of death 1970–2013 and emigration 1969–2013 was provided by Statistics Denmark. Connective tissue diseases often show involvement of interstitial lung tissue consistent with ILD and we therefore identified a connective tissue disease diagnosis as a separate reason for censoring [36]. We considered the following connective tissue diseases: arthritis rheumatica (ICD-8: 712; ICD-10: M05, M06, M08 and M09), polyarteritis nodosa (ICD-8: 446; ICD-10: M30), other necrotising vasculopathies (ICD-10: M31), systemic lupus erythematosus (ICD-10: M35), systemic sclerosis (ICD-10: M34), dermatopolymyositis (ICD-8: 716; ICD-10: 33) and other connective tissue diseases (ICD-8: 734; ICD-10: M35, M36 and J99), as recorded in the National Patient Registry 1977–2013.

### Covariates

#### Medication

Data on redeemed medical prescriptions was obtained from the Danish National Health Service Prescription Database 1995–2013. Medication was classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Nitrofurantoin derivatives (ATC code J01XE), amiodarone (ATC code C01BD01) and all antineoplastic and immunomodulating medication (ATC codes starting with "L") have ILD as a possible side-effect and were identified for the analyses.

#### Occupation

Occupation at start of follow-up defined by the Danish version of the International Standard Classification of Occupations (ISCO-88) was provided by Statistics Denmark. Occupation was classified into white-collar worker, blue-collar worker, pensioner and student. Individuals without data on occupation at any point in time were categorised and included as unclassified worker.

#### Residence

Statistics Denmark provided information on municipality of residence at start of follow-up for each individual which was classified into urbanisation categories: city, urban, rural and isolated [37]. Individuals without data on residence at any point in time were categorised as a distinct group of unknown.

### Statistical methods

The study population was followed from start of follow-up until first diagnosis of connective tissue disease, first diagnosis of hypersensitivity pneumonitis or other ILD, emigration, death or the end of study by December 31, 2013, whichever came first. Hazard ratios (HR) and 95% confidence intervals were estimated using stratified Cox regression analyses, with time since start of follow-up as the time scale. The strata were defined by each pigeon breeder, and as the referents matched on sex and year of birth, accounting for age and calendar year, no additional adjustment for these factors were performed. Analyses were adjusted for occupation (five categories) and residence (five categories) at start of follow-up. We adjusted for medication with ILD as a possible side-effect from the date of first redemption.

Analyses of hypersensitivity pneumonitis, other ILD and all analyses of the inception population were not adjusted for occupation and residence, due to a limited number of cases.

Estimates are referred to as statistically significant when $p<0.05$. All analyses and data management were performed in Stata (version 14.1; StataCorp, College Station, TX, USA).

## Results

The main characteristics of the study population are provided in table 1. Participants were 94% male and 41% were censored during follow-up (died, emigrated or were diagnosed with a connective tissue disease) (table 1). The distribution of sex, age and start of follow-up was identical for pigeon breeders and referents due to the matched design. The pigeon breeders were more often blue-collar workers and more often resided in rural areas compared with their referents. Redeemed prescriptions of medication with ILD as possible side-effect occurred with similar frequency in pigeon breeders and referents.

Pigeon breeders contributed 114 936 person-years and referents 4 566 259 person-years and the median observation period was 14 years (range <1–34 years) for both pigeon breeders and referents.

The observed incidence rate (per 100 000 person-years) of all ILDs was 77.4 among the pigeon breeders and 50.0 among the referents, corresponding to an incidence rate difference of 27.5 (95% CI 11.3–43.7) (table 2). The crude (adjusted for the matching variables) HR was 1.61 (95% CI 1.30–1.99). Additional adjustment for occupation, residence and medications with ILD as possible side-effect changed the HR only slightly (1.56 (95% CI 1.26–1.94)).

The excess risk of all ILD among the pigeon breeders predominantly stemmed from a significantly increased risk of hypersensitivity pneumonitis. The observed incidence rate (per 100 000 person-years) of hypersensitivity pneumonitis was 14.8 among the pigeon breeders and 1.0 among the referents, corresponding

TABLE 1 Demographic characteristics of 6920 pigeon breeders and their 276 800 individually matched referents 1980–2013

|  | Pigeon breeders | Referents |
|---|---|---|
| **Sex** |  |  |
| Female | 451 (6.5) | 18 040 (6.5) |
| Male | 6469 (93.5) | 258 760 (93.5) |
| **Year of birth** |  |  |
| <1930 | 1881 (27.2) | 75 240 (27.2) |
| 1930–1949 | 2578 (37.2) | 103 120 (37.2) |
| 1950–1969 | 1466 (21.2) | 58 640 (21.2) |
| 1970–1989 | 680 (9.8) | 27 200 (9.8) |
| >1989 | 315 (4.6) | 12 600 (4.6) |
| **Start of follow-up** |  |  |
| 1980–1989 | 3282 (47.4) | 131 280 (47.4) |
| 1990–1999 | 150 (2.2) | 6000 (2.2) |
| 2000–2009 | 3301 (47.7) | 132 040 (47.7) |
| >2009 | 187 (2.7) | 7480 (2.7) |
| **Censoring during follow-up** |  |  |
| Connective tissue disease | 144 (2.1) | 5416 (2.0) |
| Emigration | 110 (1.6) | 9518 (3.4) |
| Death | 2535 (36.6) | 98 529 (35.6) |
| Not censored | 4131 (59.7) | 163 337 (59.0) |
| **Occupation at start of follow-up** |  |  |
| White-collar worker | 1780 (25.7) | 102 059 (36.9) |
| Blue-collar worker | 3942 (57.0) | 127 091 (45.9) |
| Pensioner | 660 (9.5) | 25 925 (9.4) |
| Student | 278 (4.0) | 10 610 (3.8) |
| Unclassified worker | 260 (3.8) | 11 115 (4.0) |
| **Residence at start of follow-up** |  |  |
| City | 2269 (32.8) | 119 246 (43.1) |
| Urban | 1084 (15.7) | 40 836 (14.8) |
| Rural | 2385 (34.4) | 76 223 (27.5) |
| Isolated | 803 (11.6) | 25 996 (9.4) |
| Unknown | 379 (5.5) | 14 499 (5.2) |
| **Redeemed prescription of medication with ILD as possible side-effect before or during follow-up** |  |  |
| Yes | 475 (6.9) | 18 740 (6.8) |
| No | 6445 (93.1) | 258 060 (93.2) |
| **Total** | 6920 (100.0) | 276 800 (100.0) |

Data are presented as n (%). ILD: interstitial lung disease.

TABLE 2 Hazard ratios of all interstitial lung diseases (ILDs), hypersensitivity pneumonitis and other interstitial lung diseases among pigeon breeders and referents individually matched on sex and year of birth

| | Participants | Person-years | Cases | Incidence rate[#] (95% CI) | Hazard ratio (95% CI) | |
|---|---|---|---|---|---|---|
| | | | | | Crude[¶] | Adjusted[¶, §] |
| **Total population** | | | | | | |
| All ILDs | | | | | | |
| Pigeon breeders | 6920 | 114 936 | 89 | 77.4 (62.9–95.3) | 1.61 (1.30–1.99) | 1.56 (1.26–1.94) |
| Referents | 276 800 | 4 566 259 | 2281 | 50.0 (47.9–52.0) | 1 | 1 |
| Hypersensitivity pneumonitis | | | | | | |
| Pigeon breeders | 6920 | 114 936 | 17 | 14.8 (9.2–23.8) | 14.53 (8.21–25.70) | 14.36 (8.10–25.44) |
| Referents | 276 800 | 4 566 259 | 47 | 1.0 (0.8–1.4) | 1 | 1 |
| Other ILDs | | | | | | |
| Pigeon breeders | 6920 | 114 936 | 72 | 62.6 (49.7–78.9) | 1.33 (1.05–1.68) | 1.33 (1.05–1.69) |
| Referents | 276 800 | 4 566 259 | 2234 | 48.9 (46.9–51.0) | 1 | 1 |
| **Inception population** | | | | | | |
| All ILDs | | | | | | |
| Pigeon breeders | 807 | 5694 | 7 | 122.9 | 4.61 (2.10–10.15) | 4.68 (2.12–10.30) |
| Referents | 32 280 | 226 587 | 58 | 25.6 | 1 | 1 |

Data are presented as n, unless otherwise stated. Results from the total study population and the inception population are presented. The analyses of hypersensitivity pneumonitis and other ILDs, as well as the analyses for the incident members *etc*. are only adjusted for prescription of medication with ILD as possible side-effect. [#]: per 100 000 person-years; [¶]: adjusted for the matching variables by stratification; [§]: adjusted for residence, occupation and prescription of drugs with pulmonary fibrosis as possible side-effect.

to an incidence rate difference of 13.8 (95% CI 6.7–20.8). The adjusted HR of hypersensitivity pneumonitis was 14.36 (95% CI 8.10–25.44). The adjusted HR of other ILDs was 1.33 (95% CI 1.05–1.69).

The 807 pigeon breeders in the inception population contributed 5694 person-years and their referents 226 587 person-years, with a median follow-up period of 7 years (range <1–13 years) for both pigeon breeders and referents. The observed incidence rate of all ILDs was 122.9 per 100 000 person-years among the pigeon breeders and 25.6 per 100 000 person-years among the referents, corresponding to a HR of 4.68 (95% CI 2.12–10.30) when adjusting for medications with ILD as a possible side-effect. The adjusted HR of hypersensitivity pneumonitis was 113.11 (95% CI 22.82–560.66). The HR of other ILD was 0.69 (95% CI 0.10–4.99) (number of observations were few and not reported in concordance with the data protection policy of Statistics Denmark). The mean time from enrolment into the Danish Racing Pigeon Association to first diagnosis of ILD was 38.6 months (95% CI 8.0–69.2 months). Time of enrolment corresponded with start of follow-up, and among the referents time from start of follow-up to first diagnosis of ILD was 67.0 months (95% CI 56.5–77.4 months). Only seven cases of ILD occurred in the inception population, and for all estimates the confidence intervals were wide.

ILD cases had a mean 7.7 hospital contacts during follow-up. This figure was 12.8 for hypersensitivity pneumonitis and 7.5 for other ILD (data not shown). A specific ICD-10 diagnosis of bird fanciers' lung was only listed for fewer than five of the hypersensitivity pneumonitis cases (numbers not reported in concordance with the data protection policy of Statistics Denmark).

## Discussion

The present study showed a 56% (95% CI 26–94%) increased risk of all ILD and a 33% (95% CI 5–69%) increased risk for ILD other than hypersensitivity pneumonitis among pigeon breeders compared with the referent population. The risk of hypersensitivity pneumonitis was 14 (95% CI 8–25) times that of the referent population. When analyses were restricted to the 807 pigeon breeders who could be followed from first enrolment into the Danish Racing Pigeon Association, the inception population, we observed much higher estimates for all ILDs and hypersensitivity pneumonitis and no increased risk of other ILD, but the latter analysis included only a few observations.

Most previous studies have reported a prevalence of pigeon breeders' lung >10% [3, 5–7, 9, 11], while we observed a 1-year incidence of hypersensitivity pneumonitis among pigeon breeders of ~0.1%. This discrepancy probably partly reflects that previous studies defined hypersensitivity pneumonitis by acute symptoms at exposure to pigeons, while we only included patients diagnosed at a hospital, expected to comprise mainly severe or chronic cases. This is supported by the high number of hospital contacts among the cases and indicates that although many pigeon breeders experience acute symptoms of hypersensitivity pneumonitis, few develop chronic or severe disease.

The risk of hypersensitivity pneumonitis or other ILD among pigeon breeders is expected to be affected by exposure to avian antigens as well as individual susceptibility [38]. Susceptible subjects will tend to become ill earlier and resign from the Danish Racing Pigeon Association, and prevalent members are thus expected to include a higher proportion of less susceptible subjects. The acquisition of data on members prior to 2001 implies that breeders with a longer period of membership are more prone to be included in our records and in the study. We therefore analysed the risk of hypersensitivity pneumonitis and ILD among the incident members of the inception population. This analysis showed a much higher risk of hypersensitivity pneumonitis among the pigeon breeders and supports a strong health-dependent selection out of the Danish Racing Pigeon Association. The risk estimates obtained for the inception population all have wide confidence intervals due to few cases and should therefore be interpreted with some caution.

We considered all ILDs, not only cases defined as pigeon breeders' lung or hypersensitivity pneumonitis as the clinical findings may be indistinguishable from other ILD [28]. Furthermore, inhalation of avian or other antigens is part of the definition of hypersensitivity pneumonitis [15]. Defining a disease by a causal exposure blocks meaningful empirical estimation of the association with this exposure, which was the aim of this study.

The high hazard ratios observed for hypersensitivity pneumonitis are therefore expected, at least partly, to reflect the diagnosing physicians' adherence to the definition of hypersensitivity pneumonitis, and not only an effect of pigeon exposure. This is probably true even if a diagnosis of bird fanciers' lung was listed for a few of the participants only, as it may be unclear to the physician how to classify pigeon breeders' lung: *e.g.* as bird fanciers' lung (ICD-10 J67.2) or hypersensitivity pneumonitis due to organic dust (ICD-10 J67.8).

The observed increased risk of ILD other than hypersensitivity pneumonitis suggests that antigen exposure may be associated with a group of diseases, for which we know little about environmental risk factors [33, 39]. However, this result could also be generated by physicians who are not aware of the patients' exposure histories and thus do not classify cases as hypersensitivity pneumonitis but as another ILD with comparable clinical features, such as idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia [15, 19, 27–30]. Therefore, we regard the overall increased risk of ILD, and not the findings for hypersensitivity pneumonitis and other ILD, the main finding of this study.

### Strengths

This is the first study to analyse the incidence of hypersensitivity pneumonitis and other ILDs among pigeon breeders. The study population was obtained from a register of pigeon breeders and did not depend on individual participation, which may have biased earlier results [3]. The study population is, furthermore, by far the largest compared to previous studies, thereby allowing us to study the occurrence of rare diseases such as ILD and hypersensitivity pneumonitis.

Our hospital-based diagnoses in most cases reflect an extensive examination programme, as illustrated by the high number of hospital contacts recorded for the cases. Thus, we expect diagnoses of high specificity, at least compared with previous survey data.

In Denmark, pigeon exposure is solely associated with recreational breeding for racing or exhibition. This is an infrequent hobby in Denmark; it is likely that there are few pigeon breeders among the referents, and misclassification of exposure should not be an issue.

Due to continuously updated national population registers of hospital contacts, emigration and death, follow-up was complete except for the few subjects who were lost to follow-up for unknown reasons. However, this is expected to have affected <2 per 1000, and only influenced findings marginally.

### Limitations

Study participants with acute or mild symptoms are rarely referred to a hospital and will not appear in the registers that defined our outcomes.

We used membership in a racing pigeon association as our exposure metric, which is a crude, but probably very specific, measure of exposure.

Pigeon breeders are considered to be very dedicated to their sport. They may therefore refrain more often than the general population from seeking medical assistance and this may have underestimated the effect of pigeon exposure in this study [3]. Conversely, they may also be aware of the association between their hobby and lung disease and seek medical assistance earlier than others, and this may have the opposite effect.

It is widely recognised that smoking has a preventive effect on hypersensitivity pneumonitis [9, 29]. The lack of information on smoking habits inhibited us from assessing possible confounding or effect modification from smoking. However, smoking habits are associated with occupation and residence, and

adjusting for these factors may have accounted for a possible smoking effect and other factors related to socioeconomic status [40].

The analyses presuppose that incidence rates and hazard ratios are constant over time. Since our study spans >30 years, this is probably not the case, as diagnostic trends, smoking habits and pigeon breeding methods, among other things have changed over time. However, this does not affect the relative measures.

To conclude, this study shows an increased risk of ILD among pigeon breeders compared with unexposed referents. Protective measures such as respiratory protective equipment are recommended, even though ILD that leads to hospital contact remains rare among pigeon breeders.

### References

1    Reed CE, Barbee RA. Pigeon-breeders' lung: a newly observed interstitial pulmonary disease. *JAMA* 1965; 193: 261–265.
2    Calvert JE, Baldwin CI, Allen A, *et al.* Pigeon fanciers' lung: a complex disease? *Clin Exp Allergy* 1999; 29: 166–175.
3    Christensen LT, Schmidt CD, Robbins L. Pigeon breeders' disease – a prevalence study and review. *Clin Allergy* 1975; 5: 417–430.
4    Andersen P, Christensen KM, Jensen BE, *et al.* Antibodies to pigeon antigens in pigeon breeders. Detection of antibodies by an enzyme-linked immunosorbent assay. *Eur J Respir Dis* 1982; 63: 113–121.
5    Banham SW, McSharry C, Lynch PP, *et al.* Relationships between avian exposure, humoral immune response, and pigeon breeders' disease among Scottish pigeon fanciers. *Thorax* 1986; 41: 274–278.
6    Bourke SJ, Carter R, Anderson K, *et al.* Obstructive airways disease in non-smoking subjects with pigeon fanciers' lung. *Clin Exp Allergy* 1989; 19: 629–632.
7    Carrillo T, Rodriguez de Castro F, Cuevas M, *et al.* Effect of cigarette smoking on the humoral immune response in pigeon fanciers. *Allergy* 1991; 46: 241–244.
8    Rodríguez de Castro F, Carrillo T, Castillo R, *et al.* Relationships between characteristics of exposure to pigeon antigens. Clinical manifestations and humoral immune response. *Chest* 1993; 103: 1059–1063.
9    Baldwin CI, Todd A, Bourke SJ, *et al.* IgG subclass responses to pigeon intestinal mucin are related to development of pigeon fanciers' lung. *Clin Exp Allergy* 1998; 28: 349–357.
10   Charitopoulos K, Gioulekas D, Sichletidis L, *et al.* Hypoxemia: an early indication of pigeon breeders' disease. Clinical and laboratory findings among pigeon breeders in the Salonica area. *J Investig Allergol Clin Immunol* 2005; 15: 211–215.
11   McSharry C, Dye G, Ismail T, *et al.* Quantifying serum antibody in bird fanciers' hypersensitivity pneumonitis. *BMC Pulm Med* 2006; 6: 16.
12   Uzun O, Yilmaz DK, Sunter AT, *et al.* The prevalence of "pigeon breeder's disease" in a Turkish city and review of the literature. *Lung* 2011; 189: 243–250.
13   Hansen NC, Siersted HC. Allegisk alveolitis blandt fynske dueholdere. [Allergic alveolitis among pigeon breeders in the county of Funen]. *Ugeskr Laeger* 1990; 152: 25–28.
14   Fink JN, Schlueter DP, Sosman AJ, *et al.* Clinical survey of pigeon breeders. *Chest* 1972; 62: 277–281.
15   Lacasse Y, Assayag E, Cormier Y. Myths and controversies in hypersensitivity pneumonitis. *Semin Respir Crit Care Med* 2008; 29: 631–642.
16   Fink JN, Sosman AJ, Barboriak JJ, *et al.* Pigeon breeders' disease. A clinical study of a hypersensitivity pneumonitis. *Ann Intern Med* 1968; 68: 1205–1219.
17   Richerson HB, Bernstein IL, Fink JN, *et al.* Guidelines for the clinical evaluation of hypersensitivity pneumonitis. Report of the Subcommittee on Hypersensitivity Pneumonitis. *J Allergy Clin Immunol* 1989; 84: 839–844.
18   Zacharisen MC, Schlueter DP, Kurup VP, *et al.* The long-term outcome in acute, subacute, and chronic forms of pigeon breeder's disease hypersensitivity pneumonitis. *Ann Allergy Asthma Immunol* 2002; 88: 175–182.
19   Selman M. Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clin Chest Med* 2004; 25: 531–547.
20   Chan AL, Juarez MM, Leslie KO, *et al.* Bird fancier's lung: a state-of-the-art review. *Clin Rev Allergy Immunol* 2012; 43: 69–83.
21   Ohtani Y, Saiki S, Sumi Y, *et al.* Clinical features of recurrent and insidious chronic bird fancier's lung. *Ann Allergy Asthma Immunol* 2003; 90: 604–610.
22   Bourke SJ, Banham SW, Carter R, *et al.* Longitudinal course of extrinsic allergic alveolitis in pigeon breeders. *Thorax* 1989; 44: 415–418.
23   Pérez-Padilla R, Salas J, Chapela R, *et al.* Mortality in Mexican patients with chronic pigeon breeder's lung compared with those with usual interstitial pneumonia. *Am Rev Respir Dis* 1993; 148: 49–53.
24   Solaymani-Dodaran M, West J, Smith C, *et al.* Extrinsic allergic alveolitis: incidence and mortality in the general population. *QJM* 2007; 100: 233–237.
25   Lacasse Y, Selman M, Costabel U, *et al.* Classification of hypersensitivity pneumonitis: a hypothesis. *Int Arch Allergy Immunol* 2009; 149: 161–166.
26   Lacasse Y, Girard M, Cormier Y. Recent advances in hypersensitivity pneumonitis. *Chest* 2012; 142: 208–217.
27   Spagnolo P, Rossi G, Cavazza A, *et al.* Hypersensitivity pneumonitis: a comprehensive review. *J Investig Allergol Clin Immunol* 2015; 25: 237–250.
28   Morell F, Villar A, Montero MA, *et al.* Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013; 1: 685–694.

29  Costabel U, Bonella F, Guzman J. Chronic hypersensitivity pneumonitis. *Clin Chest Med* 2012; 33: 151–163.

30  Grech V, Vella C, Lenicker H. Pigeon breeder's lung in childhood: varied clinical picture at presentation. *Pediatr Pulmonol* 2000; 30: 145–148.

31  Morell F, Roger A, Reyes L, *et al.* Bird fancier's lung: a series of 86 patients. *Medicine (Baltimore)* 2008; 87: 110–130.

32  Edwards JH, Trotman DM, Mason OF, *et al.* Pigeon breeders' lung – the effect of loft litter materials on airborne particles and antigens. *Clin Exp Allergy* 1991; 21: 49–54.

33  Patterson KC, Rose CS. Hypersensitivity pneumonitis. *In*: Broaddus VC, Mason RJ, Ernst JD, *et al.*, eds. Murray and Nadel's Textbook of Respiratory Medicine (Sixth Edition). Philadelphia, W.B. Saunders, 2016; pp. 1153–1164.

34  Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc* 2007; 82: 812–816.

35  Selman M, Lacasse Y, Pardo A, *et al.* Hypersensitivity pneumonitis caused by fungi. *Proc Am Thorac Soc* 2010; 7: 229–236.

36  Solomon JJ, Fischer A. Connective tissue disease-associated interstitial lung disease: a focused review. *J Intensive Care Med* 2015; 30: 392–400.

37  Kristensen IT, Kjeldsen C, Dalgaard T.Landdistriktskommuner – Indikatorer for Landdistrikt. [Country District Municipalities – Indicators for Country Districts]. Aarhus, Aarhus University, 2006.

38  Wu C, Chen Y, Yang X, *et al.* Correlation of macrophage inflammatory protein-1α single gene polymorphisms with the susceptibility to pigeon breeder's lung in Chinese Uygur population. *Int J Clin Exp Med* 2015; 8: 13732–13739.

39  Demedts M, Wells AU, Antó JM, *et al.* Interstitial lung diseases: an epidemiological overview. *Eur Respir J* 2001; 32: Suppl. 2s–16s.

40  Osler M, Holstein B, Avlund K, *et al.* Socioeconomic position and smoking behaviour in Danish adults. *Scand J Public Health* 2001; 29: 32–39.