# Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry

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## Summary

**Background** The risk that a positive smoking history in lung donors could adversely affect survival of transplant recipients causes concern. Conversely, reduction of the donor pool by exclusion of donors with positive smoking histories could compromise survival of patients waiting to receive a transplant. We examined the consequences of donor smoking on post-transplantation survival, and the potential effect of not transplanting lungs from such donors.

**Methods** We analysed the effect of donor smoking on 3 year survival after first adult lung transplantation from brain-dead donors done between July 1, 1999, and Dec 31, 2010, by Cox regression modelling of data from the UK Transplant Registry. We estimated the effect of acceptance of lungs from donors with positive smoking histories on survival and compared it with the effect of remaining on the waiting list for a potential transplant from a donor with a negative smoking history donor, by analysing all waiting-list registrations during the same period with a risk-adjusted sequentially stratified Cox regression model.

**Findings** Of 1295 lung transplantations, 510 (39%) used lungs from donors with positive smoking histories. Recipients of such lungs had worse 3 year survival after transplantation than did those who received lungs from donors with negative smoking histories (unadjusted hazard ratio [HR] 1·46, 95% CI 1·20–1·78; adjusted HR 1·36, 1·11–1·67). Independent factors affecting survival were recipient's age, donor–recipient cytomegalovirus matching, donor–recipient height difference, donor's sex, and total ischaemic time. Of 2181 patients registered on the waiting list, 802 (37%) died or were removed from the list without receiving a transplant. Patients receiving lungs from donors with positive smoking histories had a lower unadjusted hazard of death after registration than did those who remained on the waiting list (0·79, 95% CI 0·70–0·91). Patients with septic or fibrotic lung disease registered in 1999–2003 had risk-adjusted hazards of 0·60 (95% CI 0·42–0·87) and 0·39 (0·28–0·55), respectively.

**Interpretation** In the UK, an organ selection policy that uses lungs from donors with positive smoking histories improves overall survival of patients registered for lung transplantation, and should be continued. Although lungs from such donors are associated with worse outcomes, the individual probability of survival is greater if they are accepted than if they are declined and the patient chooses to wait for a potential transplant from a donor with a negative smoking history. This situation should be fully explained to and discussed with patients who are accepted for lung transplantation.

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See Online for appendix

## Introduction

Lung transplantation was first done in a few selected patients with end-stage lung disease in the late 20th century. At first, donor selection criteria were strict; only young donors with near-perfect gas exchange who did not have other potential risk factors such as a history of cigarette smoking were accepted.[1,2] As transplantation became an established treatment,[3] donor selection criteria had to become less strict in an attempt to balance supply and demand and reduce the substantial mortality of patients on the waiting list.[4–15] Because the donor pool is drawn from the general population, it would be expected to include donors with both positive and negative smoking histories.[16] Some lung transplantation candidates could themselves have smoking-related lung disease, whereas others might have avoided active and passive smoking to prevent progression of their lung disease.

The media has criticised transplantation units because of reports of deaths after transplantation of lungs from donors with positive smoking histories, and guidelines recommend that recipients should be better informed about donor-associated risks.[17] Smoking has several adverse pulmonary effects, including permeability changes, airflow obstruction, parenchymal loss, and increased cancer risk, all of which can be reversed, partly, by smoking cessation. In view of the known hazards of cigarette smoking, some potential recipients might choose to exclude themselves from the smoking proportion of the donor pool. However, reduction of the pool by refusal to use organs with a specific but prevalent characteristic could increase the risk of waiting-list mortality, which could decrease overall and individual benefits of listing for transplantation. Thus, the effect of donor smoking history on outcomes for transplant recipients and the possible effects of exclusion of the lungs of donors with positive smoking histories are causes for concern. We aimed to establish the risks associated with transplantation of lungs from donors

with positive smoking histories and to estimate the effects of non-acceptance of such organs.

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## Methods

### Study design and setting

Adult lung transplantation in the UK is provided by five designated centres, which have primacy of organ allocation within a specified geographical region. All patients on the transplantation waiting list are registered centrally with National Health Service Blood and Transplant. Donor lungs that become available within a centre's area are first offered to that centre, and then on a rotational basis to the other centres until a suitable recipient is identified. Factors taken into account for decisions within centres are blood-group compatibility, donor–recipient tissue and antigen–antibody incompatibilities, donor and recipient size, urgency, time on waiting list, and whether one or two lungs is available for transplantation. Specific selection of a recipient is at the discretion of the accepting centre. People making decisions about donor lung acceptance carefully examine chest radiographs, bronchoscopic and macroscopic lung appearances, and gas exchange.

Lungs accepted for transplantation were retrieved by teams from designated centres by pulmonary arterial flushing of cold preservative solutions or whole-donor cooling with cardiopulmonary bypass. Lungs were transported in a hypothermic inflated state for surgical implantation. The decision to undertake single or double lung transplantation was at the discretion of the transplantation centre. Postoperative care and immunosuppression were at the centre's discretion, but included a calcineurin inhibitor, an antimetabolite such as azathioprine or mycophenolate, and corticosteroids. Post-transplantation survival and other data were gathered by the UK Transplant Registry.

Approval for use of patient-identifiable data was obtained under the provisions of Section 251 of the National Health Service (NHS) Act 2006, as regulated by National Information Governance Board. Transplantation data were initially gathered on the basis of presumed consent, but since Oct 1, 2005, informed consent was sought when the patient was registered for transplantation.

### Effect of donor smoking on post-transplantation survival

We analysed data for all 1295 first adult lung-only (excluding heart–lung) transplantations done with lungs from 1221 donors after brain death in the UK between July 1, 1999, and Dec 31, 2010. In all donors, detailed demographic, social, clinical, and laboratory data were obtained prospectively. This information included smoking history and an estimate of the daily cigarette consumption (but not pack-year consumption) from the donor's relatives or general practitioner. We compared the prevalence of a positive smoking history in lung donors with data for 7689 UK solid-organ donors after brain death during the same period.

We excluded transplantations when donors had an unknown smoking history (n=73). Transplantations were assigned to the modal group if no information was available on recipients' ventilation status (nine), presence of diabetes (nine), use of inotropes at the time of transplantation (three), creatinine clearance (one), whether they were in hospital or an intensive-care unit before the procedure (four), and whether the recipient and donor differed in cytomegalovirus status (22). Cases with unknown donor (three) or recipient (five) height and unknown bilirubin concentrations at time of registration (20) were assigned the median value. Missing data for total ischaemic time (108) were imputed from the median total ischaemic time estimated from complete data for that transplantation centre. 11 patients

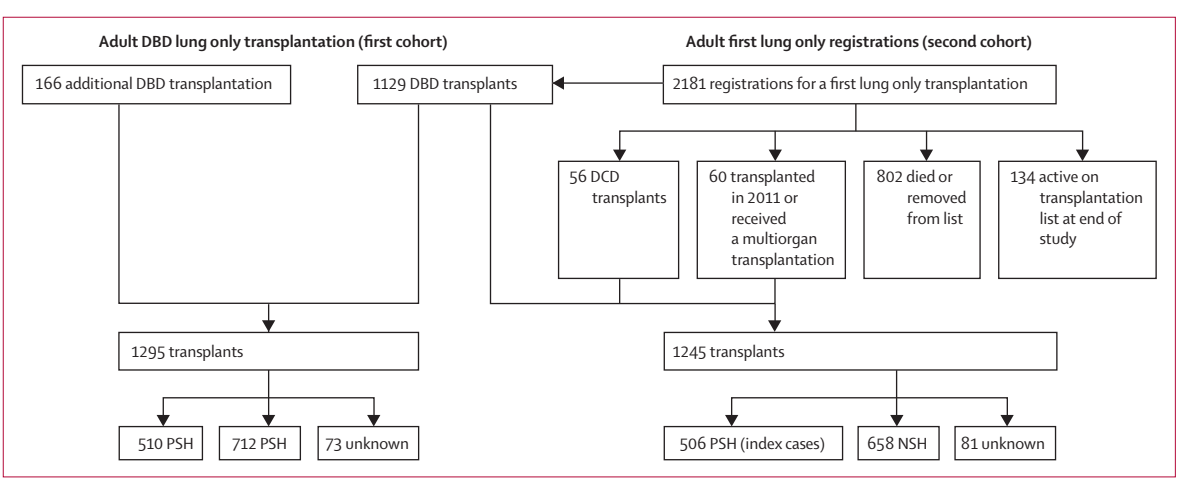


***Figure 1:*** **Flow of patients through the transplantation waiting list and breakdown of cohorts***

DBD=donors after brain death. DCD=donors after cardiac death. PSH=positive smoking history. NSH=negative smoking history. *Includes patients registered on the transplantation list before July 1, 1999 (n=75), patients registered for a heart or lung block (44), patients who received a transplant but were not registered for transplantation with National Health Service Blood and Transplant (42), patients classified as paediatric at registration but adult at time of transplantation (four), and patients registered outside the UK, but treated at a UK centre (one).


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(1%) had unknown survival after transplantation. Survival follow-up for both waiting-list registrations and all other transplantations was 100%.

The primary outcome was 3 year survival after transplantation, which was defined as time from first transplantation to death. Patients who survived for longer than 3 years (1095 days) were censored at 3 years. The survival time of patients alive on April 30, 2011, was censored at this point. 3 year survival was selected to maximise complete follow-up and as an index of midterm outcome. Secondary outcomes were recipient's cause of death, length of stay in both hospital and intensive-care unit after transplantation, and, for double-lung recipients, highest recorded forced expiratory volume in 1 s ($FEV_1$) in the first 2 years after transplantation.

Unadjusted and adjusted survival were estimated and stratified by smoking history. To estimate any incremental dose effect, we divided donors into three groups on the basis of the number of cigarettes smoked per day (0, 1–20, and >20 per day). We examined the extent of non-linearity in other variables included in the model. These variables were split into rough quartiles.

### Analysis of exclusion of lungs from smoking donors

We analysed data for 2181 UK adult patients who were registered on the national waiting list for first lung-only transplantation between July 1, 1999, and Dec 31, 2010. Survival status to April 30, 2011, was obtained from the UK Transplant Registry and the Office for National Statistics. These patients might have had lung transplantations after the censoring date.

We used sequential stratification to assess how use of lungs from donors with positive smoking histories affected survival from waiting-list entry compared with the exclusion of such donors. This technique used observational data to emulate data from a hypothetical randomised trial, allowing outcome comparisons between patients who receive a particular treatment at a specific time and those waiting for a different treatment.

The time origin was taken to be the date of registration on the waiting list, and each lung transplantation from a donor with a positive smoking history was regarded as an index case. A stratum was then formed from each index case and a control group from all patients on the transplantation list for the same length of time (in days) or longer who were eligible to get the same lung (ie, blood-group and size compatible). Patients' survival was measured from time of transplantation of the index case. Patients who received a lung from a donor with a positive smoking history were censored at time of transplantation, because they would no longer have been eligible to receive a transplant from a donor with a negative smoking history.

The survival time of the index case was censored if they were alive at April 30, 2011. The survival times of patients in the control group were censored at either time of removal from the waiting list (if date of death unknown),

| | NSH donor transplant (n=712) | PSH donor transplant (n=510) | p value |
|---|---|---|---|
| Age | 42 (25 to 52) | 43 (32 to 50) | 0·36 |
| Male sex | 330 (46%) | 220 (43%) | 0·27 |
| Cause of donor death | | | 0·012 |
| Trauma | 123 (17%) | 66 (13%) | |
| Intracranial vascular event | 473 (66%) | 379 (74%) | |
| Other | 116 (16%) | 65 (13%) | |
| Date of transplantations | | | 0·49 |
| 1999–2002 (total n=319) | 194 (61%) | 125 (39%) | |
| 2003–06 (total n=441) | 249 (56%) | 192 (44%) | |
| 2007–10 (total n=462) | 269 (58%) | 193 (42%) | |
| Duration of mechanical ventilation (h) | 40 (31·3 to 58·6) | 40 (31·1 to 57·5) | 0·62 |
| Referral $PaO_2$ (kPa)* | 40·6 (16·8 to 62·1) | 41·4 (16·5 to 61·9) | 0·19 |
| Chest radiograph | | | 0·63 |
| Normal | 539 (76%) | 394 (77·3%) | |
| Abnormal | 92 (13%) | 67 (13·1%) | |
| Missing data | 81 (11%) | 49 (9·6%) | |
| Ischaemic time (min) | 282 (228 to 330) | 282 (228 to 324) | 0·97 |
| Estimated glomerular filtration rate (mL/min per 1·73 $m^2$)† | 90·0 (70·0 to 112·0) | 92·2 (74·5 to 112·6) | 0·29 |
| Preservation type | | | 0·81 |
| Papworth solution | 124 (17%) | 87 (17%) | |
| Core-cooling | 67 (9%) | 43 (8%) | |
| Low-potassium dextran solution | 239 (34%) | 184 (36%) | |
| Modified EuroCollins/other‡ | 282 (40%) | 196 (38%) | |
| Blood-group matching (identical) | 627 (88%) | 443 (87%) | 0·54 |
| Cytomegalovirus status | | | 0·001 |
| Donor positive, recipient positive | 152 (21%) | 123 (24%) | |
| Donor positive, recipient negative | 128 (18%) | 130 (25%) | |
| Donor negative, recipient positive | 189 (27%) | 102 (20%) | |
| Donor negative, recipient negative | 243 (34%) | 155 (30%) | |
| Sex matching | | | 0·10 |
| Donor male, recipient male | 275 (39%) | 192 (38%) | |
| Donor male, recipient female | 55 (8%) | 28 (5%) | |
| Donor female, recipient male | 130 (18%) | 79 (15%) | |
| Donor female, recipient female | 252 (35%) | 211 (41%) | |
| Ethnic origin matching | | | 0·08 |
| Donor white, recipient white | 672 (94%) | 496 (97%) | |
| Donor white, recipient non-white | 24 (3%) | 9 (2%) | |
| Donor non-white, recipient white | 15 (2%) | 5 (1%) | |
| Donor non-white, recipient non-white | 1 (0%) | 0 (0%) | |
| Donor–recipient height difference (cm) | 2 (–1 to 7) | 2 (–2 to 7) | 0·15 |
| Predicted donor TLC:predicted recipient TLC§ | 1·01 (0·92 to 1·08) | 1·00 (0·94 to 1·08) | 0·64 |

Data are median (IQR) or number (%) as appropriate. Duration of mechanical ventilation is the ventilated period from initiation to aortic clamping at retrieval. Papworth solution is a preservation flush that uses cold donor blood, albumin, and electrolyte solutions. Modified EuroCollins is an established organ preservation fluid. NSH=negative smoking history. PSH=positive smoking history. $PaO_2$=partial pressure of oxygen in arterial blood. TLC=total lung capacity. *Fractional concentration of oxygen in inspired air 1·0, positive end-expiratory pressure 5 cm water. n=642 for transplants from donors with negative smoking histories and 463 for those from donors with positive smoking histories. †n=671 for transplants from donors with negative smoking histories and 478 for those from donors with positive smoking histories. ‡A few transplants (<5%) preserved in solutions such as University of Wisconsin. Numbers are insufficient for analysis and have been included with modified EuroCollins. §Predicted TLC represents predicted total lung capacity for sex-specific height.

*Table 1:* **Characteristics of lung donors with positive and negative smoking histories**

| | NSH donor transplant (n=712) | PSH donor transplant (n=510) | p value |
|---|---|---|---|
| Age | 50 (37–57) | 53 (42–58) | 0·01 |
| Male | 405 (57%) | 271 (53%) | 0·20 |
| Recipient's diagnosis | | | 0·09 |
| Chronic obstructive pulmonary disease | 278 (39%) | 197 (39%) | |
| Pulmonary fibrosis | 131 (18%) | 122 (24%) | |
| Septic (cystic fibrosis and bronchiectasis) | 213 (30%) | 130 (25%) | |
| Other | 90 (13%) | 61 (12%) | |
| Type of transplant (double) | 499 (70%) | 335 (66%) | 0·11 |
| Previous thoracic surgery | 47 (7%) | 41 (8%) | 0·37 |
| Hospitalised at transplantation | 51 (7%) | 40 (8%) | 0·66 |
| Ventilated at transplantation | 2 (0·3%) | 2 (0·4%) | >0·99 |
| Inotropic support before transplantation | 2 (0·3%) | 1 (0·2%) | >0·99 |
| Diabetes mellitus | 96 (13%) | 66 (13%) | 0·80 |
| Body surface area ($m^2$) | 1·7 (1·6–1·9) | 1·7 (1·6–1·9) | 0·11 |
| Body-mass index ($kg/m^2$) | 22·2 (19·2–26·0) | 23·0 (19·7–26·3) | 0·02 |
| Serum bilirubin (μmol/L) | 9 (6–13) | 9 (6–14) | 0·17 |
| Creatinine clearance (mL/min) | 87·2 (72·6–107·6) | 87·3 (69·7–104·3) | 0·20 |
| Transplantation centre | | | 0·57* |
| A | 217 (30%) | 152 (30%) | |
| B | 158 (22%) | 124 (24%) | |
| C | 156 (22%) | 110 (22%) | |
| D | 50 (7%) | 48 (9%) | |
| E | 110 (15%) | 72 (14%) | |
| Other | 21 (3%) | 4 (1%) | |
| Recipient's outcome | | | |
| 30 day survival (95% CI) | 94·6 (92·7–96·1) | 90·4 (87·5–92·7) | 0·006 |
| Days in ICU | 3 (2–8) | 4 (2–10) | 0·03 |
| Days in hospital | 26 (19–37) | 29 (22–42) | 0·0008 |
| 90 day survival (95% CI) | 90·5 (88·1–92·4) | 86·6 (83·3–89·0) | 0·03 |
| Highest $FEV_1$ in first 2 years (L/s)† (BLTx only total n=834) | 2·71 (2·10–3·33) | 2·42 (2·00–3·15) | 0·002 |
| Cause of recipient's death within less than 90 days (n=139) | | | 0·39 |
| Graft failure | 20 (29%) | 18 (26%) | |
| Pulmonary infection | 4 (6%) | 11 (16%) | |
| Multisystem organ failure | 17 (25%) | 17 (24%) | |
| Vascular | 12 (17%) | 8 (11%) | |
| Malignant disease | 1 (1%) | 0 (0%) | |
| Other | 15 (22%) | 16 (23%) | |
| Cause of recipient's death on day 90 or thereafter (n=397) | | | 0·046 |
| Graft failure (including BOS and OB) | 36 (16%) | 47 (27%) | |
| Pulmonary infection | 71 (32%) | 44 (25%) | |
| Multi-system organ failure | 11 (5%) | 12 (7%) | |
| Vascular | 12 (5%) | 6 (3%) | |
| Malignant disease | 17 (8%) | 6 (3%) | |
| Other | 75 (34%) | 60 (34%) | |

Data are median (IQR) and number (%), unless otherwise indicated. Transplantation centres A–E are active centres; other represents historical activity in three units. NSH=negative smoking history. PSH=positive smoking history. ICU=intensive-care unit. $FEV_1$= forced expiratory volume in 1 s. BLTx=bilateral lung transplantation. BOS=bronchiolitis obliterans syndrome. OB=obliterative bronchiolitis. *Based on differences between the five transplantation centres. †n=430 for transplants from donors with negative smoking histories and 279 from donors with positive smoking histories.

*Table 2:* **Recipients' characteristics and outcomes by donors' smoking history**

time of transplantation from a donor with a positive smoking history, or April 30, 2011, if still alive.

### Statistical analysis

Characteristics of donor, recipient, and transplant were compared for donors with positive smoking histories or negative smoking histories by Fisher's exact test, the two-sample *t* test, or the Mann-Whitney test, as appropriate. Other candidate risk factors were identified from previous registries and published work.[3,12,18–21]

Unadjusted survival estimates, stratified by smoking history, were calculated for different times by the Kaplan-Meier estimation method and assessed with the log-rank test, as was 3 year survival (conditional on survival at 90 days and 1 year). We used Cox proportional hazards regression modelling to assess whether donor smoking affected survival of the recipient during the first 3 years after transplantation after adjustment for relevant risk factors. Variables were selected by a stepwise procedure.

To calculate the effect of exclusion of lungs from donors with positive smoking histories, we combined data from each constructed stratum and analysed them with a stratified Cox regression model. This method allowed estimation of the hazard of mortality for acceptance of a lung transplant from a donor with a positive smoking history compared with the hazard of continued waiting for a potential transplant from a donor with a negative smoking history, after adjustment for other relevant risk factors. Stratification produced separate baseline hazards for each of the strata defined by the index cases. Continuous covariates shown to have a non-linear effect were split into quartiles, and a registration-period effect (1999–2003, 2004–06, 2007–10) was included to assess the consistency of the hazard ratio (HR) with time.

### Role of the funding source

NHS Blood and Transplant hold the database for transplantation in the UK but had no role in study design, data collection, analysis, interpretation, nor writing of the report. RT, DC, and HLT had full access to all the data in the study and RSB had final responsibility for the decision to submit for publication.

## Results

During the study, there were 2181 waiting-list registrations and 1295 (880 double and 415 single) lung transplantations from 1221 donors (figure 1). Lungs were retrieved from 1614 donors—21% of the total solid-organ-donor pool (n=7689). Total yearly lung-transplantation activity increased by 25% between 2000 (130 transplantations) and 2010 (162 transplantations).

510 of 1295 (39%) of transplantations used lungs from donors with positive smoking histories; the proportion did not change with time (data not shown), but was lower than the 3497 of 7689 (45%) prevalence for all solid organs (p=0·0007). After exclusion of transplantations from donors with unknown smoking histories (n=73), donors

with positive smoking histories had similar clinical and donor–recipient matching characteristics to donors with negative smoking histories, with the exception of small but significant differences in cytomegalovirus matching status and cause of death (table 1). We noted no significant differences in donor's age, oxygenation, size matching, and ischaemic time (table 1). Recipients of lungs from donors with positive smoking histories were older and had slightly higher body-mass indices than those who received lungs from donors with negative smoking histories; other characteristics were similar between groups (table 2). Use rates of lungs from donors with positive smoking histories did not differ significantly between transplantation centres (table 2).

Unadjusted Kaplan-Meier estimates of post-transplantation survival showed inferior survival by donor history of smoking (figure 2A); median post-transplantation survival time was 4·9 years (95% CI 4·4–5·5) for transplants from donors with positive smoking histories and 6·5 years (5·9–7·2) for transplants from donors with negative smoking histories. Survival was already inferior 30 and 90 days after transplantation (table 2). The divergence of outcome was sustained: 3 year conditional survival was also inferior for recipients of lungs from donors with positive smoking histories surviving 90 days (figure 2B) and 1 year after transplantation (figure 2C).

At 3 years, the unadjusted HR for donor history of smoking was 1·46 (95% CI 1·20–1·78). During the study, 536 lung-transplant recipients died. Within 90 days, we recorded no increase in graft failure as a cause of death (table 2). After 90 days, graft failure (including bronchiolitis obliterans syndrome and obliterative bronchiolitis) was more prevalent in the cohort whose transplants were from donors with positive smoking histories than in the cohort whose transplants were from donors with negative smoking histories (p=0·096). We noted no difference between the two groups in the proportion of deaths due to malignant disease (p=0·085) (table 2).

The Cox regression model analysed all pretransplantation factors shown in tables 1 and 2 and their two-way interactions. Five risk factors were identified for 3 year survival: recipient's age, donor–recipient cytomegalovirus matching, donor–recipient height difference, donor's sex, and total ischaemic time. Donor's smoking status was then added to the model (table 3). For 3 year survival, the adjusted HR for donor's history of smoking was 1·36 (95% CI 1·11–1·67, p=0·003; figure 3A). Recipient's diagnosis was significant in univariate analysis (p=0·002). HRs relative to chronic obstructive pulmonary disease were 1·49 (95% CI 1·16–1·91) for pulmonary fibrosis, 0·92 (0·71–1·18) for cystic fibrosis and bronchiectasis, and 0·86 (0·61–1·23) for other primary disease. However, after adjustment for risk factors, recipient's diagnosis was no longer significant (p=0·16). Adjusted HRs were 1·26 (0·97–1·65) for pulmonary fibrosis, 1·07 (0·75–1·52) for cystic fibrosis and bronchiectasis, and 0·86 (0·59–1·23) for other primary disease. In the 1073 of 1222 cases for whom complete data were available without imputation, the adjusted 3 year HR for donor's history of smoking was 1·44 (1·15–1·79).

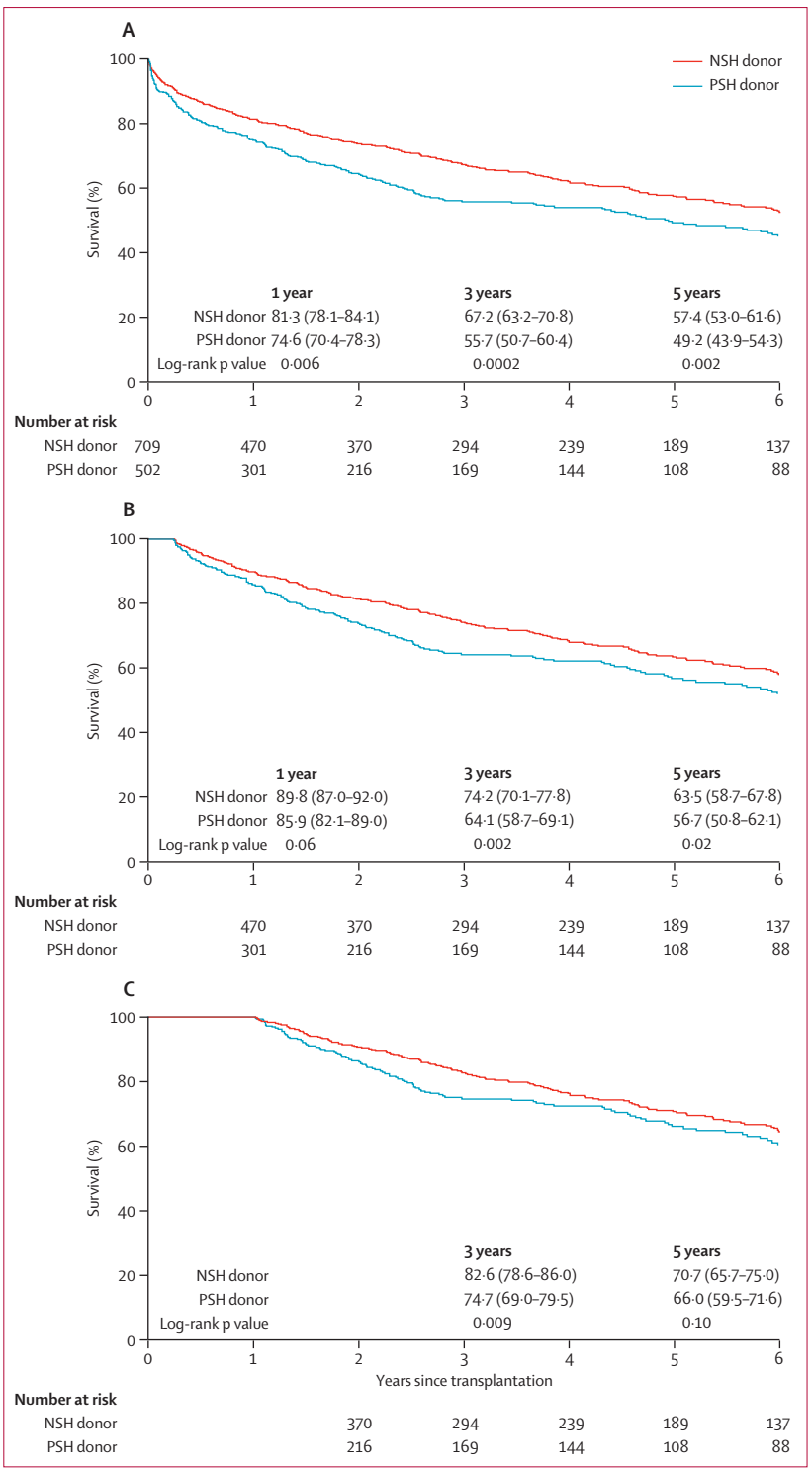


***Figure 2:*** **Kaplan–Meier unadjusted survival of patients based on donor smoking status (A) and for patients alive 90 days (B) and 1 year (C) after transplantation**
NSH=negative smoking history. PSH=positive smoking history.

Data for daily cigarette consumption were available for 457 of the 510 (90%) donors with positive smoking histories, of whom 56 (12%) were reported to smoke more than 20 cigarettes per day. Univariate analysis showed lowest survival in this category (log-rank p=0·023; figure 3B).

Recipients of lungs from donors who had smoked had longer stays in hospital and intensive-care units than did those who received non-smoker lungs (table 2). In bilateral lung-transplant recipients, the highest $FEV_1$ reported in the first 2 years after transplantation was lower in recipients of lungs from smoking donors than in recipients of lungs from non-smoking donors (table 2).

Of 2181 patients registered on the waiting list, 81 were excluded from analysis because they received lungs from donors with unknown smoking histories. Of the remaining cohort of 2100, 1164 (55%) received a transplant, whereas 802 (38%) died awaiting transplantation or were removed from the list (figure 1). An additional 134 (6%) remained on the transplantation list at time of analysis. 506 (44%) patients received lungs from donors with positive smoking histories, generating 506 strata for the sequentially stratified model. Recipients of such lungs had a significantly lower unadjusted hazard of death after registration than did those remaining on the list for a potential transplant from a donor with a negative smoking history (HR 0·79, 95% CI 0·70–0·91; p=0·0004).

| | n | HR (95% CI) | p value |
|---|---|---|---|
| Donor's history of smoking | | | 0·003 |
| Negative | 709 | 1·00 | |
| Positive | 502 | 1·36 (1·11–1·67) | |
| Recipient's age (per 10 year increase) | 1211 | 1·14 (1·05–1·24) | 0·002 |
| Donor–recipient CMV match | | | 0·03 |
| Donor negative, recipient negative | 372 | 1·00 | |
| Donor negative, recipient positive | 294 | 1·18 (0·88–1·57) | |
| Donor positive, recipient negative | 268 | 1·52 (1·14–2·01) | |
| Donor positive, recipient positive | 277 | 1·28 (0·96–1·72) | |
| Ischaemic time (per 1 h increase) | 1211 | 1·10 (1·02–1·18) | 0·02 |
| Donor–recipient height match | | | 0·003 |
| ≤–2 cm | 321 | 1·50 (1·15–1·97) | |
| –1 cm to +2 cm | 324 | 1·00 | |
| +3 cm to +7 cm | 287 | 1·21 (0·90–1·62) | |
| ≥8 cm | 279 | 0·94 (0·69–1·28) | |
| Donor's sex | | | 0·08 |
| Male | 544 | 1·00 | |
| Female | 667 | 1·21 (0·98–1·49) | |

CMV=cytomegalovirus. HR=hazard ratio.

*Table 3:* **Multivariable risk factors for 3 year survival after lung transplantation**

We identified primary disease, diabetes, and hospital status at time of registration; patient's age, sex, bilirubin concentrations, creatinine clearance, body-mass index, and $FEV_1$; and grouped registration year as significant factors (data not shown), and incorporated them into the regression model of postregistration outcome. We then added donor's smoking status and considered two-way interactions between factors. The two-way interactions between primary disease, grouped registration year, and donor's smoking history were significant, whereas interactions between smoking history and other characteristics of the donor were not and were thus not included in the model (data not shown).

Adjusted HRs for postregistration mortality by patient's primary disease for patients registered between 1999 and 2003 were 0·83 (95% CI 0·64–1·07) for chronic obstructive pulmonary disorder, 0·60 (0·42–0·87) for cystic fibrosis and bronchiectasis, 0·39 (0·28–0·55) for pulmonary fibrosis, and 0·60 (0·36–1·02) for other primary disease. These data show that the overall hazard of death after registration is lower if lungs are accepted from donors with positive smoking histories than if patients wait for transplant from a donor with a negative smoking history (figure 4).

## Discussion

Findings from this study show that recipients of lungs from a donor with a positive smoking history had lower 3 year post-transplantation survival than did recipients of lungs from non-smoking donors after adjustment for other independent factors such as recipient's age, cytomegalovirus mismatch, and increasing ischaemic time (panel). Furthermore, recipients of lungs from smoking donors were likely to spend longer in intensive-care units and hospital and could derive less functional benefit from transplantation than recipients of lungs from donors with negative smoking histories. Outcomes were worst when the donor's estimated cigarette consumption exceeded one pack per day. However, the number of life-years lost by use of lungs from donors with positive smoking histories was significantly less than the number of life-years lost if these lungs were not used. This finding applied to all patients on the transplantation waiting list, but particularly to those with septic or fibrotic lung disease. This apparently conflicting information is extremely important both for patients and for lung transplantation centres.

Increasingly, potential recipients of solid organs want to be consulted in the decision about whether to accept donated organs.[17] Possibly, patients could decline lungs from donors with positive smoking histories and choose to wait for a perfectly matched donor with few risk factors to increase their chances of post-transplantation survival. This choice would be made on the presumption that transplantation will occur before the patient dies on the waiting list or deteriorates to the extent that transplantation is no longer possible. It would also assume

that the individual's access to transplantation would not be materially affected.

However, to be registered on the waiting list, a patient must have advanced, life-threatening lung disease with progressive survival attrition. Transplantation reduces this attrition rate, but still 34% patients on the UK National Transplant list die awaiting transplant. Our data suggest that if a non-smoking donor selection strategy were adopted, the donor pool would fall by roughly 40%, which would increase waiting-list attrition rates and reduce overall survival.

Our data show that patients awaiting lung transplantation in the UK are likely to survive longer if they are willing to accept lungs from any suitable donor, irrespective of smoking history. Patients with septic lung disease have a 40% greater survival chance and those with fibrosis a 61% greater chance with an allocation strategy that includes lungs from donors with positive smoking histories than with strategies that exclude such donors.

The situation is analogous to the choice of whether a patient with chronic obstructive pulmonary disorder or pulmonary fibrosis should wait for double lung transplantation rather than accepting a single lung transplant that becomes available earlier. In chronic obstructive pulmonary disease, bilateral lung transplantation is better than monolateral transplantation.[28] In pulmonary fibrosis, which has a higher waiting-list mortality than does chronic obstructive pulmonary disease, a survival advantage is gained from waiting-list registration by acceptance of an available single lung transplant even though post-transplantation outcomes could be better if both lungs are transplanted.[29]

During the study, 20–25% of the UK population smoked.[30,31] The rates in the lung donor (39%) and total donor (45%) populations were significantly higher, and could show an association between smoking and disorders that can result in brain death.[22] Donors with positive smoking histories were less likely to have trauma as a cause of death than were non-smoking donors; however, cause of donor's death seems to have little effect on survival outcomes.[32–34] We attribute the low rate of use of lungs from donors with positive smoking histories to the application of selection criteria in clinical practice, and we assume that the highest risk donors with substantial pack-year histories were avoided on the basis of previous reports[22] or rejected because of adverse findings from gas exchange, bronchoscopy, or direct inspection. Additionally, some lungs from smoking donors were possibly selected for older recipients. Nevertheless, our rate is higher than some but not all single-centre transplantation series.[15,23]

Previous reports have suggested that the effect of smoking history is pertinent only to the early post-operative course.[22,24] In one series, a positive donor smoking history was associated with better outcomes than a negative smoking history.[23] By contrast, with a large number of patients, we have shown a sustained

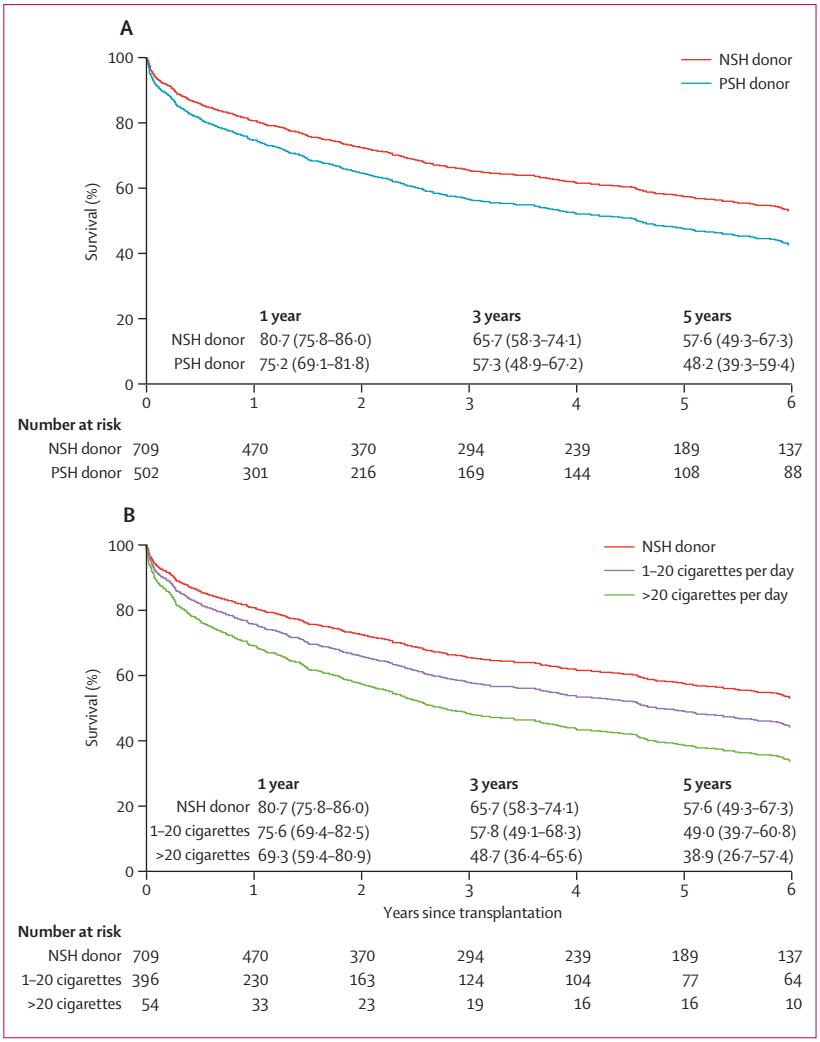


***Figure 3*: Survival of lung transplantation patients in relation to donor's smoking status (A), and numbers of cigarettes smoked (B), adjusted for other independent risk factors**
NSH=negative smoking history. PSH=positive smoking history.

independent effect, which was apparent even after 3 month and 1 year conditional survival studies. This finding was associated with an increased prevalence of late graft failure and bronchiolitis obliterans syndrome as a cause of death. Whether donor's (or recipient's) smoking affects the incidence or course of bronchiolitis obliterans syndrome is unknown. The rate of death from malignant disease did not differ between recipients of lungs from donors with positive smoking histories and those who received lungs from non-smoking donors, but the number of patients is too small to draw strong inferences from our data.

Our data did not include donor's pack-year history, which is an important risk factor for lung function deterioration in vulnerable individuals and for lung cancer. However, we noted the greatest adverse effect in current smokers with high use, which accords with data showing adverse early outcomes after lung transplantation from

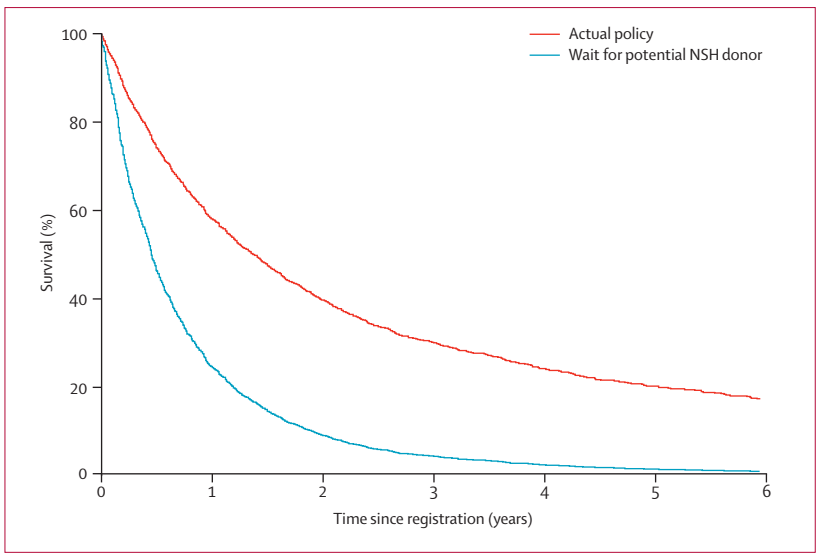


*Figure 4:* **Actual survival from waiting-list registration for patients with a diagnosis of pulmonary fibrosis listed between 1999 and 2003, and an estimated survival if lungs from donors with positive smoking histories were excluded from the donor pool and patients chose to wait for lungs from donors with negative smoking histories**
NSH=negative smoking history.

***Panel:* Research in context**

**Systematic review**
We searched PubMed, Medline, and reviews of abstracts accepted for transplantation congresses for studies published since 1955 about the effect of donors' characteristics on outcome after transplantation with the terms "lung transplantation", "smoking", and "donor". We did not restrict studies by language of publication. Three studies[22–24] investigated the effects of smoking on outcome whereas others[5–7,16,25–27] included smokers in an extended donor pool. These studies showed conflicting outcomes because donors' smoking histories were assessed differently and length of follow-up varied.

**Interpretation**
No previous study has examined the effect of not using lungs from smokers on overall survival of transplant recipients, and none has examined the implications for the individual patient of acceptance or refusal of lungs from smokers. This study establishes that, although positive donor smoking history adversely affects recipient survival, not to use such donors would increase overall mortality by compromising patient survival from waiting-list entry.

donors with pack-year histories of more than 20.[22,24] We suggest that lungs from such donors should be used with caution. Lungs from donors with positive smoking histories of less than 20 pack-years have been used in clinical transplantation for some time.[5,7,16,25] Although some evidence shows that smoking histories of more than 10 pack-years are associated with worse early outcome in recipients,[26,27] most investigators have identified an adverse effect at a pack-year history of more than 20 and the main finding has been a small effect on early mortality and length of stay in the intensive-care unit.[6,22,24,26,27]

We have shown a sustained independent effect that is accompanied by a 10% lower maximum $FEV_1$ in bilateral lung recipients in the first 2 years after transplantation. We speculate that lungs from donors with positive smoking histories have lower functional reserve before donation or greater vulnerability to immunological and infectious injuries after transplantation than lungs from non-smoking donors.

Our study is an analysis of prospectively collected registry data. History of donor's smoking is inevitably third-party information and verification is not possible. Quantification of smoking is difficult in this clinical setting, and estimates can be misclassified. Data for the smoking status of recipients before and after transplantation were not available for analysis. Criteria for selection of recipients and matching of donors were not standardised within centres, so in theory selection bias towards transplantation of lungs from donors with negative smoking histories into healthier recipients was possible. We believe that this bias is unlikely for several reasons. First, after consideration of donor–recipient matching, logistical factors, and recipient availability, the number of candidates for selection was small. Second, published reports of lung donation from donors with positive smoking histories were not compelling and unlikely to override decisions based on otherwise satisfactory matching criteria and macroscopic appearances. Finally, we noted no differences in gas exchange between donors with negative and those with positive smoking histories.

Imputation of missing data slightly decreased the HR for survival of recipients of lungs from donors with positive smoking histories compared with the complete case analysis, suggesting that our conclusions are sensitive to some extent to the treatment of missing values.

Our modelling technique assessed what might happen if donors with positive smoking histories were excluded from the donor pool but cannot anticipate what changes in clinical practice, selection of recipients, and organ allocation might occur. Importantly, we are unable to report donor pack-year smoking history, which is important in other analyses and in studies of chronic disease. Furthermore, we cannot suggest a threshold of cigarette consumption above which donor lungs should not be used for transplantation; however, we urge caution in donors who smoke more than one pack per day.

In conclusion, donors with positive smoking histories provide nearly 40% of the lungs available for transplantation. Rejection of this donor-organ resource would increase waiting-list mortality and is ill advised. However, patients should be informed that the use of such lungs could reduce their lifetime. Further research is needed to establish the threshold value for


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donor pack-year history above which the risk for the recipient increases to a degree that compromises treatment benefit. Organ-donation rates in the UK, although increasing, are inadequate to meet the needs of potential recipients, and our findings should further stimulate attempts to increase the number and use of donated organs so that more low-risk organs can be offered to recipients.

#### Contributors

RSB, RT, DC, HLT, JN, and JHD contributed to the study design and data interpretation. RT, DC, and HLT undertook the data collection, analysis, and validation. RSB drafted the first report, and all authors contributed to the final draft. Named members of the UK Cardiothoracic Advisory Group to NHS Blood and Transplant (CTAG) and the UK Association of Lung Transplant Physicians (ALTP) contributed to data collection, data interpretation, and editing of report drafts, and approved the final version.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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