Eur J Health Econ 2006 · 7:255–264
DOI 10.1007/s10198-006-0362-1
Published online: 1. July 2006

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Cost-effectiveness of the Danish smoking cessation interventions

Subgroup analysis based on the Danish Smoking Cessation Database

International research on smoking cessation interventions generally find them to be highly cost-effective in terms of cost per life-year saved or cost per quality-adjusted life-year saved compared to other preventive health care measures [1, 2, 3]. Most cost-effectiveness analyses rely on effectiveness data that come from clinical trials evaluating the relative effectiveness of especially nicotine replacement therapy (NRT) interventions. Song et al. [1] reviewed ten articles published between 1994 and 2001 and Warner [3] ten published between 1986 and 1996 evaluating the cost-effectiveness of different combinations of professional advice with NRT compared with (typically) counseling alone or placebo. With the exception of one analysis from 1987 [4] all analyses base their effectiveness estimates on literature reviews, systematic reviews, own RCTs, or meta-analyses of RCTs. Randomized controlled trials have the advantage of establishing a cause-effect relationship between input and results, but as the trials per definition take place in a closed, artificial environment, the results may not be directly transferable to a real environment with multiple influential factors. Also, in the majority of cost-effectiveness analyses, intervention costs are assessed per intervention and calculated as an average per person randomized to participate in the intervention and cost-effectiveness ratios are presented for the smoker or the group of smokers as a whole. A recent study by Godfrey et al. [5] evaluating factors influencing the relative cost-effectiveness of the smoking cessation services carried out in England was indeed based on real-life cost data collected prospectively from the English cessation units. However, data on the individual smokers participating in the cessation services were not available for the study. Often due to lack of data studies generally fail to evaluate the relative cost-effectiveness across different subgroups of smokers.

The present analysis provides a supplement to the international literature as it evaluates the "real-life" smoking cessation interventions that were implemented in Denmark between 1995 and 2001 based on data on individual smokers from the Danish National Smoking Cessation Database (DNSCD). This database has been operating since 2001 and was established to gather information on numerous smoking cessation interventions offered to smokers throughout the country by pharmacies, hospitals, municipalities, and other public or private bodies working with a preventive aim. The objective of this analysis was to assess the relative cost-effectiveness of smoking cessation interventions for different subgroups of smokers, based on the results of initial regression analyses of the individualized and detailed data from the database and a subsequent stochastic simulation of costs and effects. The perspective of the analysis was the smoking cessation units providing the interventions and to some extent the smokers participating in the interventions as participation costs and individual NRT cost were included.

The Danish National Smoking Cessation Database

All organizations providing a described smoking cessation intervention in Denmark are in principle allowed to sign a contract to join the national database. This has resulted in a great diversity of organizations reporting to the database. Contents and theoretical underpinnings of the interventions are, however, quite similar, as almost all instructors have participated in a standardized smoking cessation training course. When signing the contract with the database, the cessation units agree to complete one baseline and two follow-up standard questionnaires to the database reporting on the intervention and the participants. In return, they receive semiannual evaluation reports on the results of all units in the database and on their own individual results. The database is publicly financed and participation is free of charge for the cessation units. Al-

Table 1 Descriptive statistics

	Followed-up (*n* =1,877)	Not followed-up (*n* =1,751)	All (*n* =3,628)
Age (years)	49.6±12.0	47.5±13.6	48.6
Sex (%)			
Female	62	64	63
Male	38	36	37
Allowance to follow-up (%)			
No	<1	2	1
Yes	>99	98	99
Fagerström score	5.4±2.1	5.5±2.1	5.5±2.1
Type (% of participants)			
Individual course	17	25	21
Group course	79	72	76
Quick course	3	2	3
Other	<1	<1	<1
Setting (%)			
Hospital	29	48	38
Pharmacy	47	18	33
Other	24	34	29
Abstinence rates (%)			
All	0.31	na	0.16[a]
Men	0.32	na	–
Women	0.30	na	–
Heavy smokers	0.29	na	–
Light smokers	0.33	na	–
<35 years old	0.25	na	–
35–54 years old	0.31	na	–
55+ years old	0.32	na	–
Hospital	0.38	na	–
Pharmacy	0.25	na	–

[a] *Intention to treat*

though the majority of the cessation units are private companies, i.e., pharmacies, many counties reimburse part of the intervention costs to the pharmacies provided that they follow a standardized intervention developed by central institutions. This is part of a national and regional policy to facilitate the access to smoking cessation interventions and to avoid adverse economic incentives in the provision and evaluation of the interventions.

The interventions offered by the different organizations are typically sessions in which the instructor and the smoker meet face to face to discuss the clinical and motivational/psychological aspects of smoking and smoking cessation. The types of interventions provided are typically either group courses (7–10 participants of five or six sessions of 2 h each), individual courses (five or six sessions for a total of 2.5 h), or "quick" interventions (1–6 participants with one instructor at one or two sessions for a total of 2.5 h). NRT is also part of the intervention. NRT products can both be provided to the participants as part of the intervention and purchased by the participants themselves. At the first session the participants agree on a date on which they all stop smoking. Six and twelve months after this date the participants are asked to complete a questionnaire on their personal characteristics, smoking status, use of nicotine replacement products, etc. Furthermore, the cessation unit (the instructor) provides information on the number of smokers enrolled at the start of the course, the number of participants who have completed the entire course, the personnel time spent on preparation, direct intervention and follow-up, and the nicotine replacement products provided as part of the intervention etc. Data are gathered and recorded in the database every 6 months.

Methods

Study design

A probabilistic Markov model was used to estimate costs and gain in life-years due to participation in smoking cessation interventions. Regression analysis of the data from the DNSCD identified the factors determining abstinence and costs. These results, and age and gender differences in smoking and ex-smoking mortality risks, were then used to define subgroups that would potentially have different incremental cost-effectiveness ratios (ICER).

To determine the effectiveness of the intervention we used two measures of abstinence rate. The first measure was defined as the proportion of smoking cessation participants who reported to be sustained nonsmokers 12 months after the intervention "stop" date. Participants who had not filled in the follow-up questionnaire were disregarded in this definition which we refer to as the "reported abstinence" (RA) rate. In the second measure the baseline abstinence result of those who were lost to follow-up was carried forward to the 12 months follow-up. This means in practice that we counted all participants who had not filled in the follow-up questionnaire as smokers. This is referred to as the "intention to treat" (ITT) rate and is the most conservative measure of abstinence. **Table 1** presents the descriptive statistics from the database and the comparative statistics of the participants who were followed-up after 1 year and the participants who were lost to follow-up.

Table 1 shows that the individuals who were lost to follow-up had more or less the same characteristics as the ones who answered the follow-up questionnaire. However, more participants in hospital interventions than in other settings did not answer the questionnaire. There could be several explanations for this. If participants at hospitals more often failed to become abstinent and therefore refused to fill in the follow-up questionnaire, the ITT abstinence measure would be appropriate, and cost-effectiveness would tend to be overestimated when using the RA measure for the hospital subgroup. If the follow-up procedures were badly performed at hospitals, and if participants enrolling in

courses as patients at hospitals had a reduced ability to answer follow-up questionnaires due to a low level of functioning, it is not obvious which of the two abstinence measures would be the most appropriate. However, unfortunately, the data on the participants who were lost to follow-up were not detailed enough to allow for a drop-out analysis. We therefore chose to use the RA measure as a reference case but performed sensitivity analysis based on the ITT scenario for both the reference case and for subgroup analysis within the setting variable (hospital and pharmacy).

The intervention cost for the individual i enrolled in intervention j (j =individual, group-based, quick-stop, etc.) was calculated as follows: $Cost_{ij} = Cself_i + NRP_{ij} \times Pnicotine + instructor_{ij} / enrolled_j$, where $Cself_i$ is the individual's self-reported expenditure on nicotine replacement products. These data were provided at 6- and 12-month follow-up. NRP_{ij} accounted for the nicotine replacement products delivered to each individual participant i as part of the intervention j. Data were delivered on a consumption per week basis and the cost came from multiplying this figure with the average retail price of the mostly used nicotine replacement products. The prices, *Pnicotine,* were collected from the Danish Medicines Agency. The term $instructor_{ij}$ was the instructor personnel cost at intervention j = hourly $cost_j$ multiplied by the number of hours spent on preparation, direct intervention and follow-up (as recorded by the instructor for each intervention). As the majority of the cessation units were pharmacies (63%), we valuated the personnel cost using gross salary levels of instructors in pharmacies. This included salaries and social costs of pharmaconomists and pharmacists with 1 year and 6 years of seniority collected from the Danish Association of Bachelors of Pharmacy and the Association of Danish Pharmacists. Finally, $enrolled_j$ is the number of persons enrolled at an intervention. This figure was provided by the instructor.

All cost data were collected in 2003 Danish kroner, adjusted to the 2001 level using the official price-salary index from the Ministry of Finance, and subsequently converted to euros using the average exchange rate from 2001 (€1=7.45 crowns). A logistic regression of the probability of abstinence was then performed on the RA measure with the following covariates: sex, age, type of cessation intervention (individual, group, quick, other), setting (hospital, pharmacy, other), the Fagerström score (a measure of smoking dependency) and cigarette consumption (number of cigarettes per day). A linear regression analysis was performed on the (lognormal of) intervention costs, with the same set of covariates as in the logistic regression.

Decision analytical model

A Markov model was developed to assess the cost-effectiveness of smoking cessation interventions compared with a "no-intervention" case. The simulations were carried out in accordance with standard procedures for second order simulations and can be briefly explained as follows: We first expanded the sample size from 1,818 to 10,000 by a random sampling with replacement from the population of cessation participants (59 of the 1,818 individuals who answered the follow-up questionnaire were excluded from the analysis, as data on age, sex, or smoking status were missing). Then by running this sample through the Monte Carlo model 10,000 ICERs were calculated. Although the variance of this sample of ICERs can be used to assess variation between individuals, we focused on the uncertainty relating to a population (either the total population or a subgroup of the population) of smoking cessation participants. Therefore the first order simulation step was replicated 250 times (second order simulation). Due to the randomness in the Monte Carlo simulation we got 250 different estimates of population average ICERs. Cost-effectiveness acceptability curves (CEACs) and/or a calculation of the mean as well the 95% confidence intervals (CI) of the 250 ICERs can be used to illustrate the uncertainty relating to the population of cessation participants. We report only the results from the second order simulation. We tried running 1,000 second order replications instead of 250, but as it did not affect the results (less than 0.3% change in ICER) we used 250 second order replications throughout the analysis. Subgroup analyses were carried out as described but with the relevant subgroups of the total sample of 1,818 cessation participants.

Abstract

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Cost-effectiveness of the Danish smoking cessation interventions. Subgroup analysis based on the Danish Smoking Cessation Database

Abstract
The cost-effectiveness of smoking cessation interventions is well documented. However, most studies are based on randomized controlled trials (RCTs) and provide little information on the differences between subgroups. This study assessed the relative cost-effectiveness of smoking cessation interventions offered to various subgroups of smokers, based on real-life data. Regression analyses provided information on the factors determining abstinence and costs and led to the formation of relevant subgroups of smokers. Probabilistic Markov modeling was then used to estimate the relative cost-effectiveness of smoking cessation interventions for the entire database population and for the subgroups compared to a no-intervention case. The ICER for the base case population was estimated at €1,358. This is consistent with results from the existing literature. Group simulations showed lower ICERs for men, hospitals, and light smokers and falling ICERs with increasing age. Despite differences in the cost-effectiveness ratios between subgroups our results do not justify any kind of subgroup differentiation in a smoking prevention policy.

Keywords
Cost-effectiveness analyses · Denmark · Fagerström score · Markov modeling · Smoking cessation interventions

Table 2 Reference case model parameters

	Distribution	Mean±sd	Source
Interventions costs			
First cessation course	Sampled	–	DNSCD
Later cessation courses			
Complete	Lognormal	7.8±0.86	DNSCD
Not complete	Lognormal	7.5±0.66	DNSCD
Abstinence			
First cessation course	Sampled	–	DNSCD
Later cessation courses			
Men heavy smokers	Beta	0.32±0.019	DNSCD
Men light smokers	Beta	0.31±0.051	DNSCD
Women heavy smokers	Beta	0.28±0.015	DNSCD
Women light smokers	Beta	0.35±0.031	DNSCD
Hospital			
Probability of enrolling again after failing to quit	Point estimate (sensitivity range)	0.01 (0–0.05)	Assumption
Life-time risk of relapse	Point estimate (sensitivity range)	0.1 (0–0.5)	Assumption
Natural cessation rate (% of smoking pop.)	Point estimate (sensitivity range)	0.07 (0–0.1)	[13, 14]

*Annual risk was calculated with an assumed life expectancy of 75 years and an expected life time as smoker of 60 years (start smoking at the age of 15 years) (*DNSCD *Danish National Smoking Cessation Database)*

Table 3 Model parameters, mortality data: deaths per 1,000 (*light* <15 g cigarette tobacco per day, *heavy* ≥15 g cigarette tobacco per day)

	Former smokers	Light smokers	Heavy smokers
Men			
15–24 years	0.5	0.5	0.5
25–34 years	0.9	0.9	0.9
35–44 years	2.2	1.8	3.9
45–54 years	3.5	7.0	9.3
55–64 years	12.0	16.5	21.6
65–74 years	32.2	42.2	48.5
75–84 years	76.1	94.6	100.2
85+	205.2	269.0	267.7
Women			
15–24 years	0.2	0.2	0.2
25–34 years	0.4	0.4	0.4
35–44 years	1.2	1.8	1.4
45–54 years	3.0	5.0	5.5
55–64 years	7.9	11.2	14.6
65–74 years	19.4	29.9	33.8
75–84 years	49.5	63.5	80.4
85+	128.5	154.3	202.9

From [6], Statistics Denmark for 15–34 years.

The Markov cycle tree in **Fig. 1** gives a simplified illustration of the Markov states and transition pathways in the model. The Markov cycle length is 1 year, and a half cycle correction was performed. We used TreeAge Pro 2004 Healthcare module for model simulation.

The first strategy (smoking cessation intervention) used the information on abstinence from the dataset when simulating the first cessation attempt. Enrollees who were not abstinent after the cessation intervention or who were assumed to relapse later, were allowed to have another cessation attempt and also to become abstinent without any intervention, i.e., from a natural quit rate. The probability of abstinence in the second and third cessation attempt could not be sampled from the dataset but were assumed to equal the mean abstinence probability of the subgroup that the individual belonged to. The same held for costs associated with later attempts during the individual's lifetime. In the second strategy (no cessation intervention), we neglected the information on the first cessation attempt and the probability of becoming abstinent was assumed to be equal to the natural (background) quit rate. Model parameters in the reference case are shown in **Tables 2** and **3**. Regarding mortality risks we used the findings from Prescott et al. [6] based on Danish population study data for the older age groups. For smokers in the young age group (15–34 years of age) we assumed that smokers' risk of dying young was equivalent to that of the general population of the same age, converting mortality data from Statistics Denmark into annual mortality rates. This assumption is justified by findings presented by Doll et al. [7].

Three parameters (probability of enrolling in a new cessation course, relapse and natural quit rate) were based upon quite uncertain estimates. *Probability of enrolling again after failing to quit* was the annual chance of enrolling in a smoking cessation intervention again had the first attempt been unsuccessful, presuming that the Danish smoking cessation programs continue in their present form. This probability was estimated by dividing the annual number of new smokers being recorded in the Database by the total number of smokers in Denmark (6,600 new enrollees in the first 6 months of 2004×2/1,215 million smokers [8]). This gave an annual probability of 1% which when used in the simulation model resulted in a mean life time participation rate of two courses per participant and a maximum of four courses. This seemed to be a reasonable level. *The lifetime risk of relapse* after not having smoked for 12 months was assumed to be 10% in reference case. The 10% rate was a compromise between the relapse rates used in the literature (ranging from 0–35%) [1, 9, 10, 11]. Life time risk was converted to a (constant) annual risk using the method in [12] and an assumption of a life expectancy of 75 years and a smoking start age of 15 years. *The natural cessation rate* of 7% per annum chosen as a baseline value corresponded to the background cessation rate of the "no-intervention" control group in a Danish randomized population-based study evaluating the effectiveness of intensive and targeted smoker recruitment strategies combined with intensive smoking reduction intervention [13, 14]. We followed the guidelines from NICE and used a *discount rate* of 3.5% in the reference case and performed sensitivity analysis of 0 and 6%. Costs and life-years were discounted at the same rate.

Presentation of uncertainty

Parameter uncertainty was assessed by probabilistic sensitivity analysis and presentation of cost-effectiveness acceptability curves (CEACs). Univariate sensitivity analysis was performed on all parameters based on point estimates (the probability of enrolling in a new intervention, relapse,

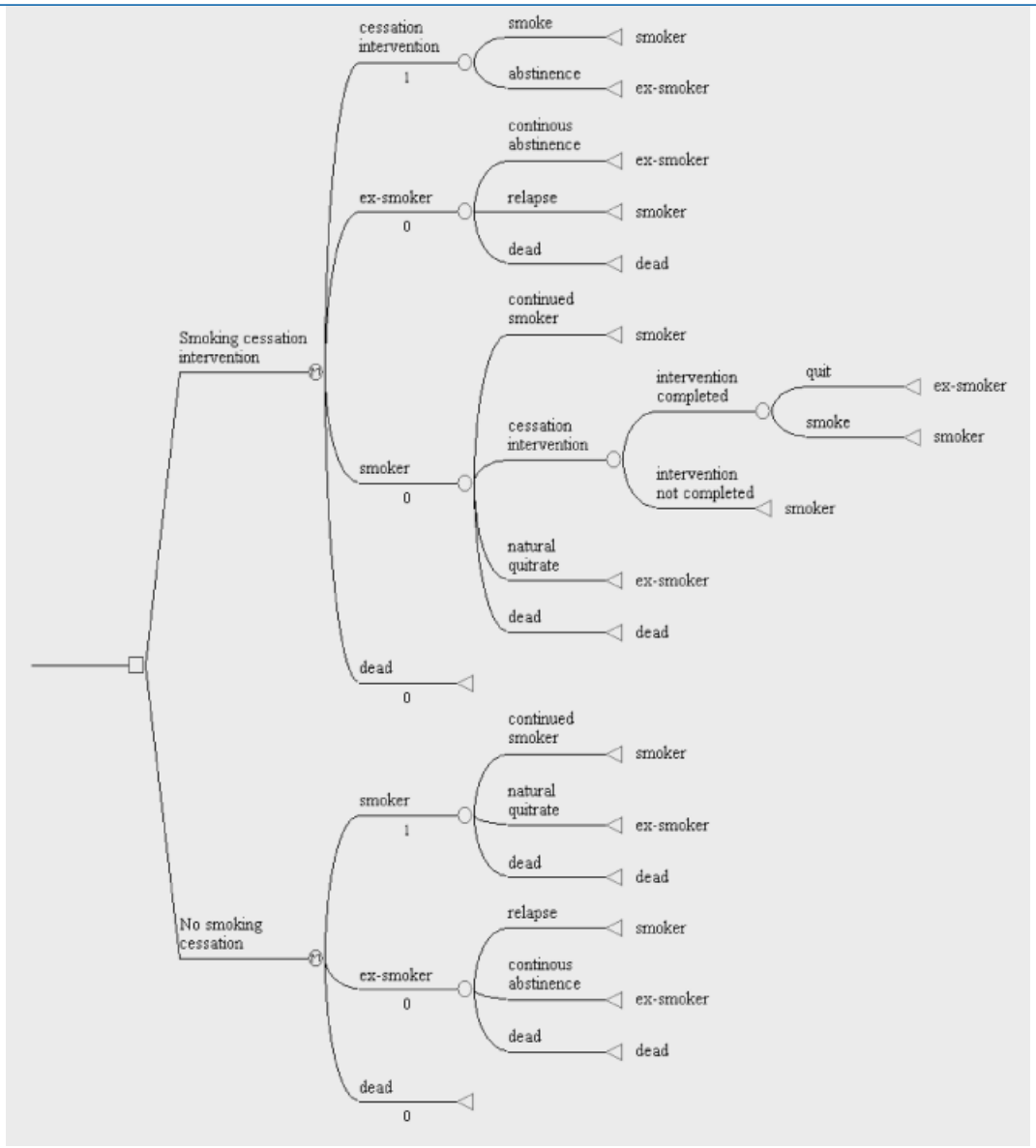

Fig. 1 ▶ Markov cycle tree

and natural quit rate), on the discount rate and on the ITT measure of abstinence.

Results

Logistic regression on the determinants of abstinence was carried out and the results are presented in **Table 4**. It can be problematic to carry out regression analysis on a dataset where all missing abstinence observations (the participants who were lost to follow up) are assumed to be smokers, because it might add a systematic measurement error and hence bias our estimates. Therefore we present regression results only for the RA abstinence measures. The results in **Table 4** show that interventions carried out at hospitals were more effective than interventions carried out at pharmacies (columns 1–3). However, this result should be interpreted cautiously because, as discussed above, the RA abstinence measure might be overestimated if many of the hospital participants who were lost to follow-up did in fact continue to smoke.

Furthermore smoking dependency, as measured by the Fagerström score was a significant covariate: the more dependent the less probability of abstinence (column 1). As our mortality data were divided into heavy and light smoker subgroups depending on tobacco/cigarette consumption, we also used tobacco/cigarette consumption as an explanatory variable in separate models. Heavy15 and heavy20 were dummy variables equal to 1 if the participant smoked more than 15 and 20 cigarettes per day, respectively. Both odds ratios (OR) were less than 1 (columns 2, 3) but only heavy20 was statistically significant; that is participants smoking more than 20 cigarettes per day had a significantly lower probability of abstinence.

Table 5 presents the results of the linear regression of cost data. To deal with the right skewness of cost data (skewness 2.95 and kurtosis 21.02), we used log transformed cost data as a dependent variable. We used the same set of explanatory variables as in the logistic regression on abstinence. The results in **Table 5** indicate that the explanatory variables gave only a moderate explanation of cost variation. However, cessation courses other than individual and group courses such as quick courses were slightly cheaper. The same held for courses carried out at county ser-

Table 4 Result of logistic regression on reported abstinence: odds ratios and 95% CI

	(1) Reported abstinence	(2) Reported abstinence	(3) Reported abstinence
Age	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Sex male	1.13 (0.91–1.40)	1.13 (0.92–1.39)	1.16 (0.94–1.43)
Type			
Individual	1	1	1
Group	1.01 (0.82–1.46)	1.05 (0.80–1.38)	1.05 (0.80–1.38)
Other	0.58 (0.29–1.17)*	0.55 (0.28–1.07)	0.54 (0.28–1.06)
Setting			
Hospital	1	1	1
Pharmacy	0.55 (0.43–0.67)**	0.52 (0.41–0.66)**	0.52 (0.41–0.65)**
County service	0.90 (0.66–1.21)	0.90 (0.67–1.20)	0.88 (0.66–1.18)
Other	0.36 (0.18–0.73)**	0.40 (0.21–0.77)**	0.40 (0.21–0.78)**
Dependency			
Fagerström	0.92 (0.88–0.97)**	–	–
Cigarette consumption			
Heavy15	–	0.80 (0.61–1.03	–
Heavy20	–	–	–0.78 (0.63 to 0.97)*
Log likelihood	–1,029	–1,100	–1,099

*P ≤0.05, **P ≤0.01

Table 5 Result of linear regression on cost data. Beta estimates and *t* value

	Ln (Cost)
Age	0.001 (0.52)
Sex male	–0.004 (–0.10)
Type	
Individual	1
Group	0.12 (2.20)
Other	–1.69* (–6.40)**
Setting	
Hospital	1
Pharmacy	0.039 (0.94)
County service	–0.123 (–2.04)*
Other	0.185 (1.90)
Cigarette consumption	
Heavy20	–0.027 (–0.73)
R^2	0.16

*P ≤0.05,**P ≤0.01

vices. Somewhat counterintuitively, group courses were found to be slightly more expensive than individual courses.

One of the main criticisms of probabilistic modeling is that it often treats parameters as independent. In the main part of our model we sampled parameters directly from the dataset and hence took the possibility of correlation between parameters into account. However, the probability estimates of abstinence and intervention costs for new smoking cessation attempts had the first been unsuccessful were identical to the probabilities which were used for the observed cessation attempt. We varied the probability of abstinence according to sex and smoking status (see **Table 2**) to take into account the significant covariance between these covariates and the abstinence we found in the logistic regression. We did not take the possibility of correlation between costs and abstinence into account because of lack of evidence of such correlation. (Running a logistic regression for abstinence with costs as covariate gave OR of 1, 95% CI 1–1) and running a linear regression with log transformed costs as dependent and abstinence as covariate gave $P = 0.556$). However, as the abstinence in the "no intervention" strategy was based on a global estimate of the natural quit rate and did not vary according to sex, age, etc. we potentially missed important covariance in this part of the model. However, unfortunately, it was not possible to obtain sufficient data to take this issue into account.

To summarize, we found that smoking dependency and cigarette consumption were significant determinants of abstinence. Hospitals had significantly higher abstinence rates and courses other than individual and group course (e.g., quick courses) and courses carried out at county services were less expensive. Mortality risks were related to sex, age and tobacco consumption. Based on the above findings we undertook subgroup analysis of the following parameters: sex, age, tobacco consumption (heavy vs. light), and setting (hospital vs. pharmacy). We disregarded quick courses and county services in the subsequent subgroup analysis because less than 1% of all interventions in the database were carried out as quick courses and only 7% were county services.

Incremental cost-effectiveness ratios

Table 6 presents the results for both the reference case and for the subgroups. The incremental cost for a life-year gained was estimated at €1,358 for the sample of smokers in the DNSCD who reported abstinence status after 1 year. The analysis of subgroups showed that while ICERs for women, heavy smokers, and participants at pharmacies only differed slightly from the aggregated results of the total sample, men, light smokers and participants at hospitals had around 15% lower ICERs. Subgroup analysis of age groups showed that participants under 35 years of age had substantially higher ICERs (€9,651 vs. €1,358 for the whole population).

Uncertainty assessment

CEACs for the various simulation results are illustrated in **Fig. 2**. The CEACs in **Fig. 2** showed relatively steep CEACs for most subgroups meaning that the estimated ICERs are subject to a relatively low level of uncertainty. The interpretation of the CEACs repeated the observation from the estimated ICERs: the probability of being cost-effective at different thresholds was higher for men, light smokers and participants at hospitals compared to women, heavy smokers and participants at pharmacies (**Fig. 2a, b**). The probability of the intervention being cost-effective approached 1 for the entire population as well as for the subgroups related to sex, setting and smoker status at a willingness to pay of approx. €2,300. The CEACs for the age groups showed that the probability of cost-effectiveness approached 1 at approx. €1,000 for participants aged 55 years and at approx. €4,000 for participants aged 35–54 (**Fig. 2c**). For participants aged under 35 years the probability of cost

effectiveness approximated 80% at a willingness to pay of €30,000 (**Fig. 2c**).

Figure 3 illustrates the results of the univariate sensitivity analysis, on the parameters based on point estimates as well as sensitivity upon the choice of abstinence measure (RA vs. ITT). The sensitivity range of the point estimates is given in **Table 2**. The level of discounting and the variation in the natural quit rate had the largest impact on changes in ICERs. Using the ITT abstinence rate instead of the RA rate resulted, as expected, in a higher ICER. This is because the abstinence rate is lower in the ITT measure (16% compared to 31%). **Table 1** showed that many participants at hospitals were lost to follow up. It was to be expected that ICERs increase for hospital participants in the ITT scenario because the missing participants were counted as smokers. **Figure 3b** shows that cost effectiveness was lower for hospitals than for pharmacies when using the ITT – the opposite of that of the RA measure. These findings suggest that the result of subgroup analysis on the setting variable must be interpreted with care.

Discussion

Comparison with other cost-effectiveness analyses

Other studies reviewing or evaluating the relative cost-effectiveness of counseling and NRT strategies compared to counseling only or "do nothing" alternatives [1, 9, 10, 11, 15, 16] reported incremental costs per life-year gained within the range of €300–9,000, and less when costs per quality-adjusted life-year were estimated. Although reservations must be made when comparing studies due to great methodological differences, we find our results consistent with those of other studies. Godfrey et al. [5] who also based their analysis on real-life data found an average cost-effectiveness ratio of £684 (approx. €990), a figure not far from our results. Cornuz et al. [15] used Monte Carlo simulation in a Markov model to compare the cost-effectiveness of counseling alone with counseling plus five different pharmacological strategies for smoking cessation for a cohort of a pack-a-day smokers (heavy smokers). Al-

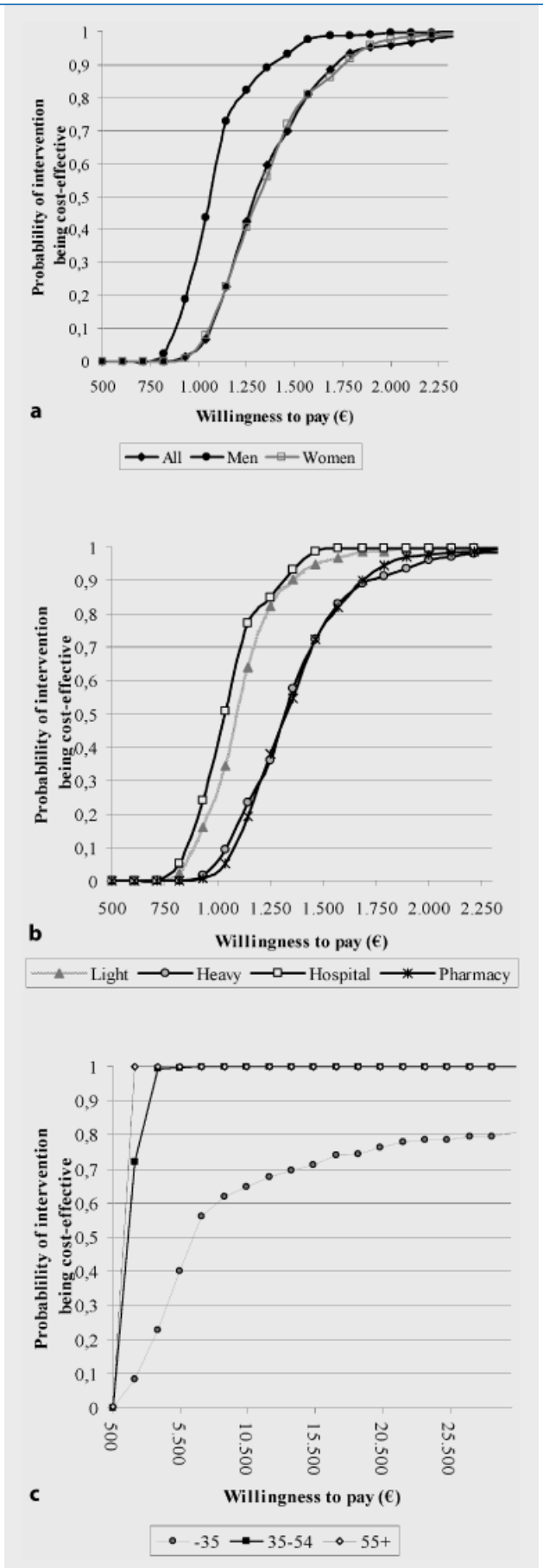

Fig. 2 ▶ Cost effectiveness acceptability curves. **a** Sex. **b** Setting and cigarette consumption. **c** Age

Table 6 Estimated incremental cost-effectiveness ratios (*ICERs*) for subgroups

	n in sample	Mean cost increase €/ personΔC[a]	Mean increase in life-years/ personΔLY[a]	Mean ICER (€)	95% CI
Reference case	1,818	450	0.35	1,358	1,320–1,396
Sex					
Men	697	423	0.40	1,090	1,065–1,116
Women	1,121	450	0.34	1,361	1,326–1,395
Smoking status					
Light	753	442	0,41	1,114	1,090–1,137
Heavy	1,065	438	0,34	1,362	1,325–1,400
Setting					
Pharmacy	882	464	0,35	1,361	1,326–1,396
Hospital	528	426	0,41	1,058	1,036–1,081
Age groups					
25–34 years	220	415	0,05	9,651	–[a]
35–54 years	954	446	0,24	1,984	1,907–2,060
55+ years	644	443	0,67	673	664–681

[a] *CIs were not estimated because second-order replicates lay in all four quadrants of the cost-effectiveness plane*
All estimates were produced by running 10,000 first-order-and 250 second-order simulations; the reported ΔC and ΔLY values are means from the 250 second-order simulations: the reported ICER is the mean of the 250 ICERs and hence does not compare to ΔC/ΔLY

though it did not use stochastic simulation, this study was probably the closest methodologically seen, to our study of the studies reviewed. The costs per life-year gained depicted in this study lay between €385 and €796 for counseling and between €1,768 and €8,799 for counseling plus pharmacological treatment. This Swiss study used a conservative estimate for ex-smoker mortality, as it was assumed that it would take an ex-smoker 25 years to regain a never-smoker's mortality risk. This was probably the main reason why these ICERs tended to be a little higher than in our study. Cornuz et al's study found that the younger have higher costs per life-year gained than the older and women higher than men, a conclusion which was consistent with our results. As mentioned above, most studies evaluating smoking cessation interventions were based on data from RCTs or meta-analyses and reviews of clinical trials. Our results were built on "real-life" data and the comparison with other cost-effectiveness studies did not show any major inconsistency between our results and results based on RCTs.

An important intermediate result was that cessation costs did not vary significantly between subgroups (except for the young age group; please see the discussion in the section on subgroup analysis). Furthermore, abstinence was significantly different only for heavy smokers and for the setting variable (pharmacy, hospital). In theory the ICER can be significantly different between two subgroups even though the two estimates in the nominator (ΔC) and denominator (ΔLY) are not significantly different from each other. The relatively modest variation in ICERs across subgroups might be explained by the low level of variability in costs and abstinence of the Danish population used in the analysis.

Three parameters were based on rather uncertain assumptions: the relapse rate, the probability of enrolling in a new course, and the natural quit rate. The relapse rate was based on an assumption of a constant annual risk which might be too simplified. More obvious relapse risks could be modeled as a function of the time as ex smoker, with a decreasing risk of relapse the longer the person had been abstinent. When using a constant rate, we might have underestimated the risk of relapse when it would happen close to the abstinence date and overestimated the risk when it would happen long after the abstinence date. As we used 1 year abstinence measures, and a Markov cycle length of 1 year, and as it is often assumed that relapse is less probable after 1 year of abstinence, this may not be a serious omission. In our model participation in more than one intervention was allowed under what we consider to be reasonable assumptions. According to our knowledge, no other studies have analyzed the likelihood of participating in more than one course and this could be an obvious area of further research. Variations in the natural quit rate did have a relatively large effect on the ICER. In our reference case, we used a relatively high level of 7%. This estimate was taken from a Danish study. Sensitivity analysis showed that reducing the natural quit rate reduced the ICER. If indeed the 7% assumption, was too high it means that cost–effectiveness was underestimated in the reference case.

Subgroup analysis

The main conclusion from the subgroup analysis was that there were only moderate differences between the subgroups except for the group of participants under 35 years of age. A possible explanation for this is that benefit gains in mortality from quitting smoking appear only at higher age. Furthermore, younger participants have a higher probability of accumulating intervention costs because they have a higher accumulated probability of participating in more than one cessation course. Another explanation for the relative high ICER for the young smokers is that life-years for older participants are not being devaluated as much as young participants due to discounting. The mean gain in life-year without discounting was estimated to 0.15 life-year (not reported in the table), compared to 0.05 with the reference case discount rate (**Table 6**). Another explanation is that even though significance of the age variable was not robust in the logistic regression (**Table 4**), participants under 35 years of age had a lower abstinence rate (RA abstinence for this group is 25% compared to 31% for the population mean). The fact that we sampled from the sub population did affect the CEA results.

Policy implications

We estimated an ICER around €1,300 for the population in the Danish smoking cessation database, with a variation between €600 and €10,000 when subgroups were analyzed independently. Cost-effectiveness analyses are not automatically part

of the decision-making process in Danish health care policy formulation, and there exists no official Danish threshold for willingness to pay for a life-year. However, there is consensus between researchers of health economics that smoking cessation intervention is indeed a very cost effective intervention, providing additional health value for little money compared to other health care interventions [3], and our study only confirmed this point of view. Indeed our study showed that conclusions from randomized controlled efficacy-trials can be replicated in our model with effectiveness data from a nationwide, real-life, decentralized, multisetting intervention. Our study also indicated that the intervention was robustly cost-effective for different sex, age groups, for heavy and light smokers and in the hospital as well as in the pharmacy setting. A study from the United Kingdom [17] analyzed a number of decisions by the National Institute of Clinical Excellence (NICE) to recommend different health interventions in order to investigate whether a cost-effectiveness threshold was applied and the potential influential factors to such a threshold. Of the 26 interventions that NICE had recommended, "smoking" had the lowest ICER of approx. €630 (£ 430) (incremental cost per quality-adjusted life-year gained) and "Orlistat" the highest of approx. €67,000 (£46,000). A review of Australian authorities' decisions on reimbursement showed an acceptance ceiling for cost-effectiveness ratios in Australia of around €25,000 ($AUS 42,000). Thus compared to cost-effectiveness ratios that are accepted in policy recommendations in both the United Kingdom and Australia, smoking cessation intervention ICERs lay far below the acceptance ceilings, and investing in smoking cessation should be highly recommended from a cost-effectiveness viewpoint. Our study demonstrated that interventions offered to men, older persons, and light smokers are more cost-effective than interventions offered to women, young persons, and heavy smokers. Despite the differences in cost-effectiveness it should be borne in mind that for all subgroups, with ICERs far below international thresholds, investing in smoking cessation interventions is still highly cost-effective.

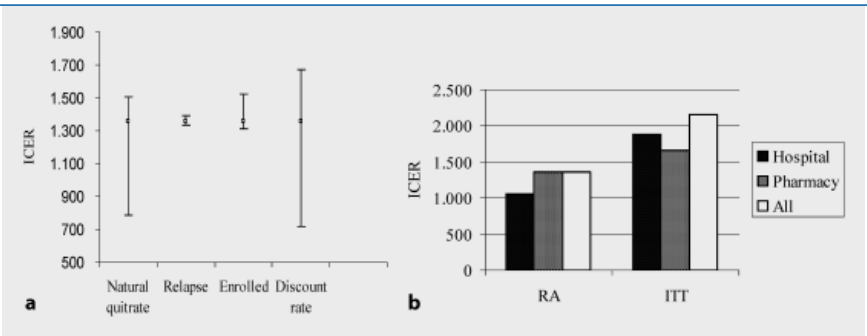

Fig. 3 ▲ Sensitivity analysis. **a** Sensitivity analysis on parameters based on point estimates. The box shows the reference case ICER and the whiskers show ICERs with high and low sensitivity parameters. See **Table 2** for sensitivity intervals. **b** Sensitivity analysis. Reported abstinence (*RA*) vs. intention to treat (*ITT*). Remember that almost one-third of the participants were enrolled in courses at other settings than pharmacy and hospital (see **Table 1**). The ICERs for 'All' were therefore not necessarily surrounded by the ICERs of hospitals and pharmacies

Generalisability of results

The majority of the smoking cessation instructors involved in the interventions, i.e., all group course instructors, received the same training developed and performed by employees from the Danish Cancer Society who are involved in smoking prevention at a national level. The aim of the centralized training is to offer a standardized intervention throughout the country with the possibility of cross-unit evaluation regardless of type of cessation unit and health professionals involved. The basis for the training was the central guidelines on smoking prevention developed by the same institution, recommending that smoking cessation interventions should be offered as a combination of cognitive therapy inspired by the transtheoretical model and motivational interviewing [18] and nicotine replacement therapy for individual smokers or groups of smokers.

Furthermore, although many of the units are private pharmacies and the instructors are pharmaconomists, that is, bachelors of pharmacy, other professionals such as nurses are involved in interventions at hospitals and other clinical settings. As the salary levels of nurses and pharmaconomists are similar, we did not differentiate between these professionals in our cost model. Also, since the training is general, following a centrally developed – and to a certain extent internationally recommended – standard it may in principle be offered by any professional who follows the training to become a smoking cessation instructor and the costs of the instructor time should be seen in this perspective. The extent to which our results can be generalized to other settings, for example, to other countries, depends on the local organizational set-up of the intervention: do other countries offer a similar combination of counseling and NRT? What are the qualifications of the instructors in other countries? Furthermore, the choice of instructor personnel and the intensity of the NRT package used are factors which influence costs and thus the comparability with the Danish setting. Finally, a very relevant issue which remains yet to be analyzed in relation to generalizability is the extent to which specific cultural or individual factors may influence the participation rate and effectiveness, for example, of individual vs. group interventions. This issue is however, far beyond the scope of this analysis.

Weaknesses and further research

The present study adds two dimensions to the literature on smoking cessation cost effectiveness: the use of real life data, and the subgroup analysis which was possible due to the availability of individualized data in the database. Regarding the use of real life data an important weakness of our study compared to the studies based on controlled trials, is the choice of comparator, the "do nothing" strategy, which is the "real life" equivalent to an RCT placebo control. We assumed that smoking cessation in the "do nothing" strategy took place at zero costs. This is probably rather optimistic, as in the real life, smokers do make self-initiated and self-directed quit-smoking attempts, using, for exam-

ple, NRT. This obviously adds costs to the "do nothing" strategy, making our ICER for smoking cessation interventions even more favorable.

Finally, it should be mentioned that our cost-effectiveness analysis, as with most of the reviewed cost-effectiveness analyses, did not include an estimate of life-time health care costs and productivity losses and gains for present and former smokers. It has been argued that since non-smokers and former smokers live longer, their life time health care costs are higher than those of smokers [19]. It has also been documented that this conclusion is highly dependent on which costs one includes [20]. Since including health care costs in our analysis would influence our conclusion in a negative or positive way depending on which costs were included or excluded from the analysis, we felt that it would not be feasible to consider this aspect of smoking cessation.

One disadvantage of the presented approach was that we were not able to test whether subgroups differ significantly from each other. This could have been done using a regression approach to CEA [21, 22]. Normally, regression based CEA is used when cost and effect measures are available at individual level for both strategies. This was not the case in our study because the comparator strategy (the do nothing strategy) was simulated rather than observed. As it is not clear how the regression approach should be carried out when the effect measures and the comparator strategy are simulated rather than observed, we did not follow this approach. One fear could be that uncertainty estimates in the regression analysis become a function of the number of simulation carried out in the Markov model.

Conclusion

The present study adds two dimensions to the existing literature on cost effectiveness of smoking cessation. The first dimension is the use of real life individual level data. The second dimension is the availability of data to perform subgroup analysis. Our results are consistent with cost-effectiveness analyses based on RCT data, indicating that there is a not a great difference in terms of results between using RCT data or real life data. The results also suggest a modest variation in ICERs between sex and age subgroups, between hospital- and pharmacy-based interventions, and between heavy and light smokers. Subgroup simulations showed that ICERs were lower for men than women, lower for hospitals than pharmacies and lower for light than heavy smokers. However, the main conclusion to be drawn from the subgroup analysis is that the differences do not justify any kind of subgroup differentiation in a health prevention policy: smoking cessation is cost effective for all analyzed subgroups.

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Acknowledgements. T.E., H.M., H.H.J., and H.H. designed the data collection in collaboration with the other members of the Danish National Smoking Cessation Database (DNSCD) Steering Committee. M.R. handled the DNSCD data collection. H.H.J. drafted the design of the economic analysis. L.B. carried out the literature review and collected, with assistance from N.T.K., model parameters from other sources than the DNSCD. K.R.O. designed and carried out the modeling and data analysis with assistance from L.B.. L.B. and K.R.. O. drafted the manuscript with assistance from H.H.J., and all authors critically reviewed and finally approved the manuscript. The study was supported financially by the Danish Ministry of the Interior and Health, The Danish Institute for Health Services Research and the Clinical Unit of Health Promotion at Bispebjerg Hospital. We thank statistician Andreas Habicht for data management assistance and Susanne Reindahl Rasmussen from DSI for helpful discussions on the analysis. An earlier version of the manuscript was presented at the 2005 IHEA Conference, and we thank the session participants for their interest in the analysis.

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