

Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional study.

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Abstract

Background. CT-Scan is currently under assessment for the screening of non-malignant asbestos-related diseases and lung cancer and potential applications among former exposed subjects have been reported. However, to date no consensus exists as to how to select high-risk asbestos-exposed populations suitable for such screening programs.

Methods. A screening program of non malignant asbestos-related diseases by CT-scan was conducted among asbestos-exposed volunteers in France. Precise assessments of asbestos exposure were obtained by occupational hygiene measurements and a job-exposure matrix. Several parameters were calculated (time since first exposure, duration, intensity and cumulative exposure to asbestos). Predictive parameters of prevalence and incidence were then estimated by standard logistic and a complementary log-log regression models.

Results. 1011 subjects were recruited in this screening program among them 474 (46.9%) presented with pleural plaques and 61 (6.0%) with asbestosis on CT-scan. Time since first exposure ($p<0.0001$) and either cumulative or mean exposure ($p<0.0001$) showed significant and independent associations with both pleural plaques and asbestosis prevalence and pleural plaques incidence.

Conclusion. Our findings confirmed the role played by time since first exposure and cumulative (or mean) exposure in asbestos-related diseases and strongly suggest to include these parameters in high-risk populations suitable for screening of these diseases.

(199 words)

Introduction.

CT-scan is without contest the reference tool for diagnosis of asbestos-related diseases as this technique is both more sensitive and more specific than chest X-rays [1]. An international consensus conference [2] has recommended the use of CT-scan in exposed population for clinical individual evaluation or research purposes with respect to pleural plaques and asbestosis. Several countries, who develop specific compensation funds for non malignant asbestos related diseases such as in USA [3] or in France [4], recommend the use of CT-scan. The prevalence of both pleural plaques and asbestosis is associated with time since first exposure to asbestos, intensity level, duration or cumulative exposure to asbestos depending on the studies [1, 5, 6], but these criteria remain entangled. Moreover, the majority of published studies are based on chest X-ray data, resulting in difficulties and imprecision for the estimation of dose-response relationships for asbestos-related diseases [7]. Thus in the few papers predicting the prevalence and incidence of pleural plaques [8] or asbestosis [9], none used CT-scan data and the shape of the dose-response relationships remains uncertain [10].

Recommendations for potential applications of CT scan in lung cancer screening among asbestos exposed subjects have also been reported [6]. Among the conclusions of this conference, the need to assess the respective role of known risk factors of lung cancer (latency and cumulative exposure to asbestos, smoking characteristics, age, asbestos related radiographic findings) was highlighted in order to define populations suitable for such screening programs.

A prediction model based on detailed exposure information and lung diseases assessed by CT-scan would therefore be of potential public health importance in identifying such high-risk groups in which screening for both non-malignant and malignant

respiratory diseases would be particularly beneficial. Some authors have proposed definitions of high lung cancer risk population based on prediction models including different tobacco consumption status [11] but, to our knowledge, no one included asbestos exposure. As an example, some authors [12] defined high risk subjects in a CT-scan lung cancer screening program by an empiric combination of age, smoking status and duration of asbestos exposure. A widespread CT-Scan screening of occupationally asbestos-exposed populations could become a major public health option, only if it is possible to define reliably high-risk groups.

The present paper presents the results of such a modelling based on a large population with detailed asbestos exposure information and systematic CT-scans.

Population and methods

Eligibility criteria

Subjects from two populations were included in the present study. First, retired workers who participated in a screening program for asbestos-related diseases that was instated in 1991 in Normandy (France). Preliminary reports and detailed methods were previously published [13, 14] concerning this population. Second, active workers aged 50 or more recruited in the same industrial activities as the retired workers, mainly asbestos textile and friction materials fabrication, insulation and energy production. This second population was added following the national consensus conference held in 1999 in Paris [15].

All subjects, both retired and active workers, had to be free of previous involvement in systematic HRCT screening campaigns in their companies, and not known to carry asbestos-related diseases prior to the time of inclusion. Retired subjects were recruited either by mail from their former employers or through local information meetings. Active workers were informed by their occupational physicians. All included

subjects gave their written informed consent. All investigations were performed in four hospitals located in Rouen, Le Havre, Caen and Flers.

Clinical and Occupational data

All subjects underwent a standard interview in order to obtain occupational, medical and smoking histories. For occupations implying asbestos exposure in one or several companies, dates of hire and end of assignments as well as durations of exposure were recorded. For some subjects who had worked in an asbestos textile and friction material plant, a quantitative assessment of occupational exposure was obtained using a specific Job Exposure Matrix (JEM) elaborated from airborne measurements collected annually between 1959 and 1999 in the various workshops of the plant. For all other subjects, estimation of asbestos-exposure level associated with each job was assessed using published airborne measurements available in the French Database Evalutil [16] according to the calendar period of exposure and the reported usual tasks.

For all subjects, a cumulative exposure index (CEI) was then calculated and was expressed in fibers/ml.years. It was obtained by summing over all job positions held, with reference to the occupational calendar established in the interview, products of typical job exposure level (in fibers/ml) by job duration (in years). An average exposure index was calculated by dividing the CEI by the duration of exposure. Time since first exposure to asbestos, duration of exposure (years), cumulated exposure index and the average exposure index were used in the statistical analysis as asbestos exposures descriptors.

Diagnosis of pleural plaques and asbestosis from imaging

Conditions of CT scan were previously described in detail [14]. Briefly, all subjects underwent a conventional or spiral CT-scan without contrast material depending on the

date of inclusion. CT-scans done after 2002 follow the recommendations published by the French Thoracic Imaging Society [17] for the use of CT-scan in asbestos-exposed subjects. For retired subjects, all examinations included at least six high-resolution millimetric sections in prone position and full inspiration, five of which were equally spaced between the carina of trachea and the bottom part of the costophrenic angles, whereas the remaining section was half way between the carina of trachea and the extreme pulmonary apices. For active workers, acquisitions slices were conducted in prone position only if the first sequence showed interstitial abnormalities.

Reading was carried out using a standard grid describing the features of (a) asbestos-related pulmonary fibrosis lesions (i.e., interlobular septal thickening, intralobular lines, honeycombing, subpleural curvilinear lines and ground-glass opacity), and (b) pleural fibrosis lesions (i.e., pleural plaques and diffuse pleural thickening), as well as (c) the pulmonary opacities associated with pleural changes (i.e., parenchymal bands and rounded atelectasis), as described by several authors [18, 19]. Pulmonary fibrosis was assessed from the HRCT interstitial abnormalities that persisted in prone position. Pleural plaques presence were rated (no, possible, certain) and only certain pleural plaques were considered for the present study. Both pleural plaques and parenchymal abnormalities were independently rated by three readers from a five-reader panel who were blinded to the subject's medical data and occupational characteristics. The median of the three rates was retained as the final rate.

Statistical methods

The prevalence was analyzed using a standard logistic model. From this analysis, a predictive model can be obtained for the population prevalence of a population with a given asbestos exposure.

A second analysis tries to infer the effect of the asbestos exposure on the incidence of pleural plaques based on the model developed by Järholm [8] which we extend by incorporating the quantitative exposure assessment obtained in the present study. This model presupposes that the probability of belonging to this study population does not depend on the disease status (given the exposure), and that the exposure has stopped at the time of data collection. Assuming that the incidence is a power function of a lagged time since first exposure multiplied by a function of the exposure (either cumulative exposure and/or mean exposure and/or duration of exposure or the log transformed versions of these variables), it can be identified from the prevalence data (see appendix).

The different (non-nested) models we compared using the Akaike information criterion.

Results

Table 1 presents the age and smoking structure as well as all collected variables with respect to the asbestos exposure, according to the diagnosis of the CT-scan among the 1011 subjects included in this study. As expected, subjects with pleural plaques or asbestosis are older than the healthy population. We note that while the numbers of never smokers are lower among the cases, the number of pack years is similar in the three groups.

All asbestos exposure indices, except age at first exposure, are larger when either pleural plaques or asbestosis have been diagnosed. It is noteworthy that the differences in time since first exposure correspond approximately to the age differences between the groups.

Table 2 presents two logistic models for the prevalence of pleural plaques as a function respectively of the mean asbestos exposure level and the cumulative exposure. Figure 1 shows graphically how the first of these models translates in estimates of the prevalence by time since first exposure and selected values of the mean exposure. These models were obtained by successively including all asbestos variables and several potential confounders (age, obesity, period of birth). None of these variables reached a 10% significance levels. It is particularly notable that when fitting duration of exposure, not only was it far from significant, but the fitted coefficient was lower than one, indicating that if anything, longer durations are associated with lower risks after adjustment on time since first exposure and mean exposure (or cumulative exposure). This might explain why the cumulative exposure model (Model 2 of Table 2) which includes both mean exposure and exposure duration fitted the data slightly less well than Model 1 which is based singly on the mean exposure.

The models were also fitted within the two recruitment subpopulations and to the subpopulation of all subjects with a CEI less than 250 fibers/ml.years . All results were compatible with the models presented in Table 2.

When estimating an incidence, using a complementary log-log regression, the models with the best fit included linear exposure concentration and/or cumulative exposure rather than log-transformed variables. As for the logistic model the duration of exposure did not significantly contribute to the fit and was dropped. With respect to the minimum latency time, all models with a minimum latency between 6 and 12 years yielded a virtually identical fit.

Table 3 presents the fit of the complementary log-log regression with a minimal latency of 10 years and its interpretation as a model for the incidence of pleural plaques.

The parameters of the incidence curve can be interpreted in terms of absolute and relative risks. E.g the yearly incidence rate for 2 f/l and 20 years since first exposure is estimated at $0.00823 \cdot 10^{0.340} \cdot \exp(0.0690 \cdot 2) = 2.1\%$. Similarly according to model 1, the relative risk of a subject with a 10 f/l mean exposure compared with a 2 f/l mean exposure is $\exp(0.069 \cdot (10-2)) = 1.74$. The minimum observed latency for a subject with pleural plaques was 16 years. We can note that the fit of the logistic model to the data as assessed by the Akaike information criterion, seems to be very close to the complementary log-log model.

Finally, Table 4 presents the best-fitting logistic models of the prevalence of asbestosis. Although the coefficients of a model including time since first exposure and cumulative exposure are statistically significant, the best fitting model according to the Akaike information criterion includes age and mean exposure.

When fitting a complementary log-log regression, some coefficients were negative, indicating that some hypotheses on which this model is based are not met.

Discussion

This population is characterized by an asbestos exposure assessment based mainly on historical measures and the use of CT-scan for the diagnosis of asbestos-related diseases. These findings allow us to precisely analyse the relationships between the asbestos exposure parameters and effects. To our knowledge, it is the first time that such data are published. Concerning the prevalence of pleural plaques, we found that the most important independent variable is time since first exposure characterizing the disease latency. Both cumulative exposure and mean exposure appear to be also independently associated with pleural plaques, without any great differences between the two models. No other parameter showed a statistical association with the presence of pleural plaques including duration of

exposure or tobacco consumption expressed in pack-years. Modeling the incidence of pleural plaques showed again the same significant variables.

Most of published studies reported a positive dose-response relationship between prevalence of pleural plaques and asbestos exposure [1]. Time since first exposure is known to be strongly associated with pleural plaques in the literature [10]. Jakobsson et al. [20] reported that time since first exposure was more correlated to prevalence of pleural plaques assessed on chest X-rays than cumulative exposure, after adjustment on age and smoking status. More recently, Koskinen et al. described a prevalence of bilateral pleural plaques ranging between 1.2% (latency < 16 years) to 32.2% (latency \geq 40 years) in a large study of construction, shipyard and asbestos industry workers [5]. In this study, a lesser positive correlation with the duration of asbestos exposure was also reported. Erhlich et al. [21] showed in multiple regression analysis that only time since first exposure was significantly related to prevalence of pleural plaques, but neither cumulative exposure nor duration of exposure. Our results however showed that both mean (or cumulative) exposure and time since first exposure are determinants for the prevalence. This discrepancy may be explained by the better precision of our exposure data.

Asbestosis is also associated with latency [5] but the main parameter seems to be cumulative exposure [20, 21, 22]. A threshold was estimated about 25 fibres / ml.years [7] that confirmed experimental and epidemiological data. However, some cases were described below this threshold, mainly in case of very intense exposure [21]. It is generally recognized that the latency of asbestosis is shorter with increasing intensity of exposure [23]. Again, we found that the time since first exposure and cumulative exposure are independent factors of the prevalence of asbestosis. According to our results, we propose to define subjects at high risk of developing asbestos-related diseases on the basis of time since first exposure and mean or cumulative exposure.

The question of the optimal periodicity of CT-scan follow-ups in asbestos workers remains unsolved. In our study, no estimates could obtain for the incidence of asbestosis, but incidence model of pleural plaques shows that the increase is modest over the years. For example, according to the model including only time since first exposure and mean exposure, the yearly incidence increases from 0.8% 10 years after the onset of exposure to 2.4% 30 years after exposure onset for a mean exposure of 1 fibre/ml.. This finding agrees with the literature, even if only few papers were published on this topic. In a cohort survey (> 20 years) of insulators, the incidence of pleural plaques was estimated between 15% to 21% and between 4 to 10% for parenchymal abnormalities [21]. Accordingly to our findings, the optimal periodicity of medical survey by CT-scan for these non malignant asbestos related diseases may range between 5 to 10 years (4% to 24% of new cases of pleural plaques accordingly to our data), that it is less frequent than the recent statement of the ATS [1].

With respect to lung cancer, recent studies showed that prediction models including cumulative asbestos exposure [24] or time since first exposure provide the best fit [25]. Although our data are not directly relevant for predicting lung cancer, they show qualitatively similar conclusions for pleural plaques and asbestosis. The relationships between pleural plaques and lung cancer are still controversial [26, 27]. Recently, Cullen et al. [28] showed that “pleural plaques on the baseline radiograph and abnormal baseline flow rate were strong independent predictors of subsequent lung cancer.” On the other hand several publications reported a strong association between asbestosis and lung cancer, even taking into account level exposure to asbestos [29, 30]. Thus, our findings strengthen the case for defining high-risk exposure groups, to be included preferably in screening programs, based on cumulative asbestos exposure and time since first exposure.

However, some limits of our study have to be discussed.

First, the population used in this study is not representative of the general population as only asbestos-exposed volunteers were included. Moreover, we enrolled only supposed healthy subjects for the screening results, which entailed a selection of these subjects. E.g., we can assume that the most severe cases of asbestosis in these populations were diagnosed before inclusion on a clinical basis and were thus not included in the study population. This, as well as the small number of cases, may probably explain the difficulties to fit the data and obtain a valid model for the asbestosis incidence. However, if this selection may influence the parameter values in the model of estimated prevalence for asbestosis in our sample, this selection bias is probably minor for pleural plaques as this disease is usually asymptomatic [31].

Another point is the technique of HRCT used in this program. We have already discussed in a previous publication [14] that a 6 slices protocol is considered adequate for the diagnosis of asbestosis and had been recommended [2]. For pleural plaques, the use of mediastinal windows and a continuous acquisition of data minimized the risk of missing pleural abnormalities.

Two basically equivalent statistical models were used to model the prevalence of pleural plaques and asbestosis in this population. The logistic regression model is the standard epidemiological method, mostly because its coefficients can easily be interpreted in terms of odds ratios. The complementary log-log regression is more rarely used in epidemiology except in some survival modeling. However, fitting this model on these data allowed us, given some assumptions, to get a mathematically simple expression for the incidence. The most important assumption is that the possibility of being observed (i.e. being included in the population) does not depend on the presence of pleural plaques, respectively asbestosis. It has already been discussed that this does not seem to be a problem for pleural plaques but certainly is one for asbestosis, hence the inconsistent

results for its interpretation. The second assumption is that the asbestos exposure does not vary with time for each subject when the prevalence was assessed. As most workers are retired and as asbestos is now banned, this does not appear to be a major issue. The last assumption is that the incidence curve takes a specific functional form which states that the incidence is zero until a given minimum latency and increases as a power function of (time since first exposure minus minimum latency), multiplied by a basic incidence depending only on the past asbestos exposure.

Conclusion.

Time since first exposure and mean (or cumulative) exposure to asbestos were both independently and significantly associated to the prevalence and, to the incidence of pleural plaques and asbestosis. These two parameters have to be included in definitions of high risk subjects for non malignant asbestos related diseases. If the evaluation of the lung cancer screening procedures by Low-Dose CT-Scan confirms his effectiveness, it will be necessary to narrow the definition of people suitable for such screening programs. Among existing models of lung cancer prediction, no one included asbestos exposure to our knowledge. Our results indicate that both latency and mean (or cumulative) exposure should be discussed if these prediction models are to consider asbestos exposure.

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Table 1 – Asbestos exposure and confounders among males according to disease status

	Healthy subjects (n=476)		Pleural plaques (n=474)		Fibrosis (n=61)	
age	60.6	8.0	64.0	8.2	64.8	9.2
Non-smokers (n(%))	156	32.8%	116	24.5%	18	23.1%
Ex-smokers (n(%))	244	51.3%	301	63.5%	47	60.3%
Pack-years	21.7	19.2	20.2	16.8	21.2	19.6
Smokers (n(%))	76	16.0%	57	12.0%	13	16.7%
Pack-years	29.7	24.3	25.7	20.7	26.2	26.7
Time since first Exposure (y)	34.3	8.6	39.5	9.2	38.5	9.8
Age at first Exposure (y)	26.3	9.0	24.6	7.9	26.3	8.3
Duration of Exposure (y)	22.8	9.0	25.1	9.4	23.4	9.6
Cumulative Exposure (y.f/L)	88.9	92.4	137.0	140.8	143.3	135.4
Mean Exposure (f/L)	3.9	3.4	5.5	5.1	6.5	5.6

Results are given as means and standard deviations or as numbers and percent, as relevant.

Table 2 – Modelling the prevalence of pleural plaques using logistic regression

	Model 1			Model 2		
	OR	CI	P	OR	CI	P
Time since first exposure (y)	1.075	1.059-1.092	<0.001	1.067	1.051-1.083	<0.001
Mean exposure (f/l)	1.114	1.077-1.153	<0.001			
Cumulative exposure (10 y.f/l)				1.036	1.023-1.049	<0.001
Akaike Information Criterion		1228.0			1235.4	

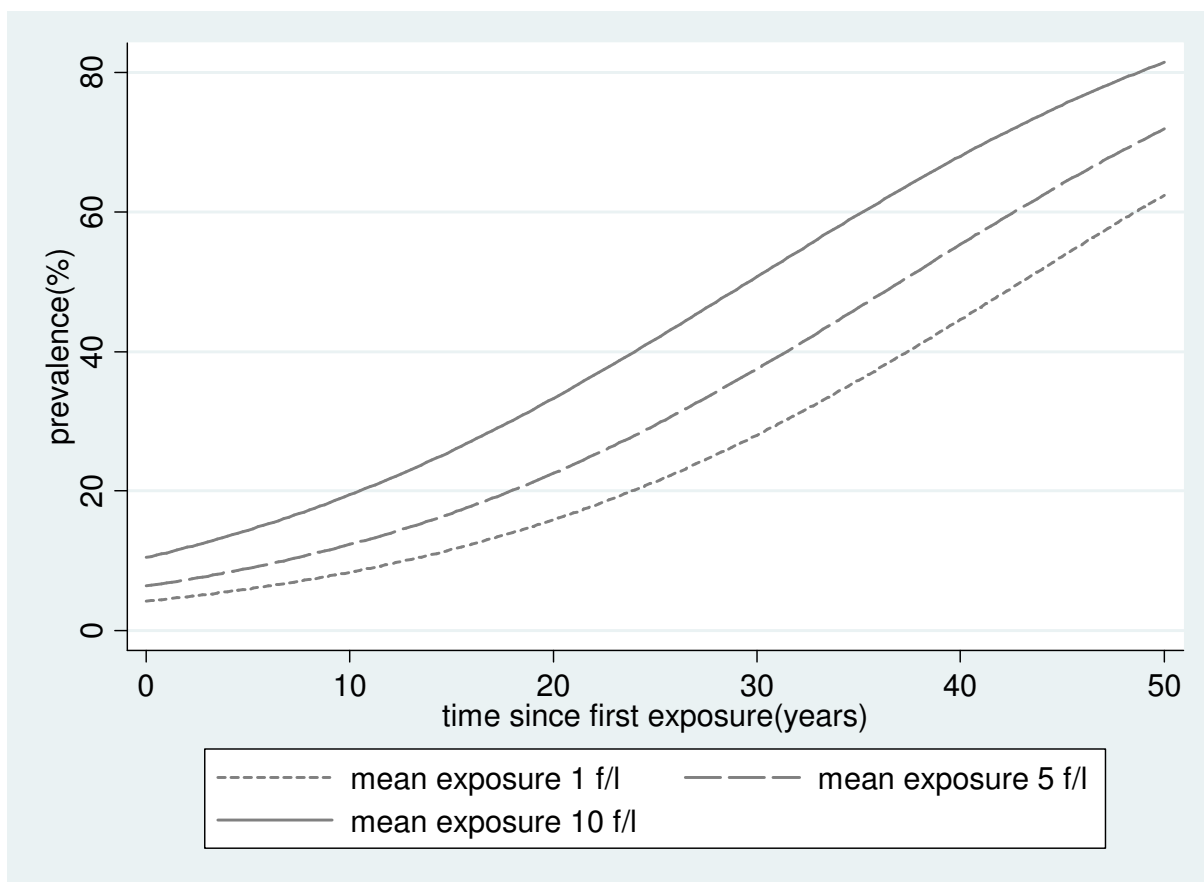
Table 3 Modelling the incidence of pleural plaques using a complementary log-log regression

	Model 1			Model 2		
	coefficient	CI	P	coefficient	CI	P
Intercept $\text{Log}(k/(\alpha+1))$	-5.093	-6.098, -4.089	<0.001	-4.553	-5.519, -3.588	<0.001
Log time since first exposure	1.340	1.045,1.635	<0.001	1.201	0.913,1.490	<0.001
Mean exposure (f/l)	0.069	0.049,0.090	<0.001			
Cumulative exposure (100 y.f/l)				0.211	0.142,0.281	<0.001
Akaike Information Criterion	1230.3			1239.4		
Fitted Incidence model	$0.00823 \times (t-10)^{0.340} \times \exp(0.069.f)$			$0.0127 \times (t-10)^{0.201} \times \exp(0.00211.cf)$		

Table 4 – Modelling the prevalence of asbestosis using logistic regression

	Model 1			Model 2		
	OR	CI	P	OR	CI	P
Time since first exposure (y)	1.03	1.00-1.06	0.038			
Mean exposure (f/l)				1.09	1.04-1.14	<0.001
Cumulative exposure (10 y.f/l)	1.03	1.01-1.04	0.001			
Duration of exposure (y)						
Age (y)				1.07	1.03-1.11	<0.001
Akaike Information Criterion		446.0			417.8	

Figure 1 : Fitted prevalence of pleural plaques according to time since first exposure, and selected values of mean asbestos exposure over the exposed job periods.



Appendix : Inferring an incidence model based on prevalence data

This derivation follows the mathematical model proposed by Järholm (1992)

Let us assume that the incidence model has following mathematical form

$$I(t)=k.(t-w)^\alpha .f^\beta .d^\gamma \quad \text{if } t>w \quad (1)$$

The constant k may depend on other characteristics like smoking or age at first exposure, but is not allowed to depend on time. The latter condition is not an intrinsic assumption, but the model cannot be fitted using standard software unless it is met.

This means in particular that while age cannot be fitted but the period of birth is allowed. This has also the consequence that this model may only be applied assuming that the exposure has ceased at the time of the disease assessment by TDM.

We postulate the existence of a cohort exposed to asbestos, for which each subject was submitted to a TDM at some time t since his/her first exposure to asbestos. We assume further that the fact that this disease assessment was independent of the actual disease status.

Let us further denote by $N(t)$, the number of exposed subjects in this cohort at time t and $P(t)$ the disease prevalence (i.e. the prevalence of pleural plaques) at this time.

At time t , $N(t)(1-P(t))$ subjects do not show pleural plaques and are therefore at risk of developing pleural plaques.

In a Δt time span following t , the number of new cases can be written as $N(t).\Delta P(t)$ on one side, and, if Δt is a short time span, as the $\Delta t.I(t).N(t)(1-P(t))$ on the other side.

Thus we have $N(t).\Delta P(t)= \Delta t.I(t).N(t)(1-P(t))$

Cancelling out $N(t)$ and dividing both terms by Δt , we get

$$\frac{\Delta(1-P(t))}{\Delta t} = (1-P(t))I(t)$$

Letting Δt go to zero and solving the differential equation, we obtain

$$\ln(1-P(t)) = \int -I(u)du = -k.f^\beta .d^\gamma \int_w^t (u-w)^\alpha du = \frac{-k}{\alpha+1}.f^\beta .d^\gamma .(t-w)^{\alpha+1}$$

Taking the natural logarithm of the opposite, we obtain following formula

$$\ln(-\ln(1-P(t))) = \ln\left(\frac{k}{\alpha+1}\right) + (\alpha+1)\ln(t-w) + \beta.\ln(f) + \gamma.\ln(d) \quad (2)$$

This is the formula for a complementary log-log regression of the prevalence data which is easily fitted with any software (e.g. SAS, Stata, GLIM) providing a generalized linear modelling framework. The independent variables fitted are, in this case, the logarithms of the exposure variables and the logarithm of the lagged time since first exposure.

When the fitted independent exposure variables consist in a single untransformed exposure concentration f , the incidence is

$$I(t) = k \cdot (t-w)^\alpha \cdot \exp(\beta f) \quad \text{if } t > w$$

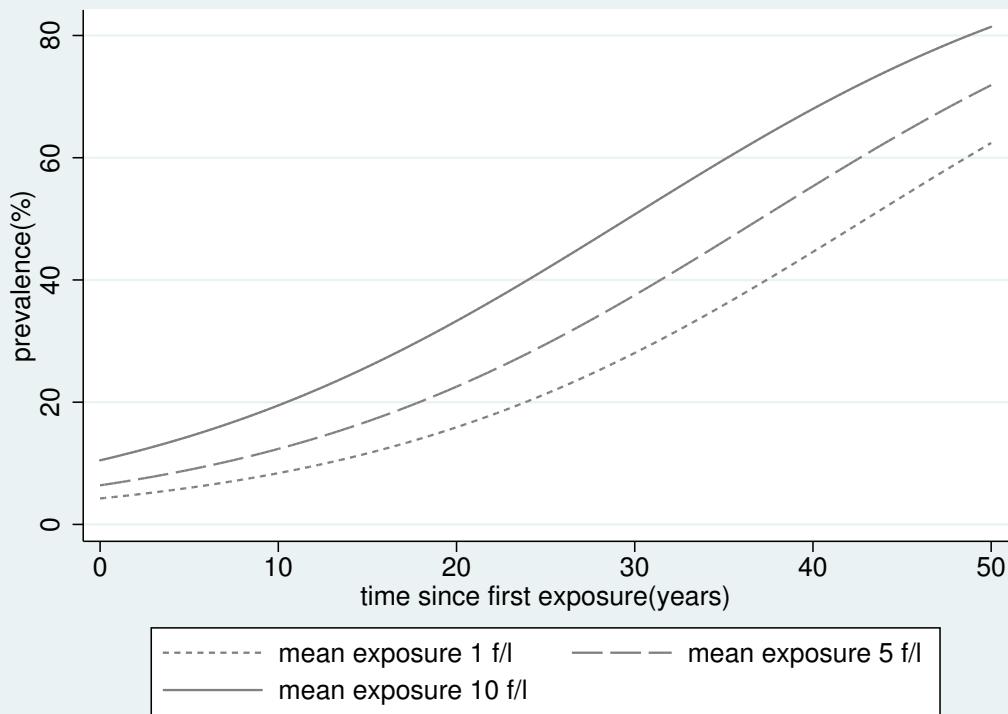


Figure 1