EPHOR

Exposome tools for a healthy working life

H2020 program	Grant agreement number 874703
Project start date: Jan 1st 2020	Duration: 66 months
Project Coordinator: Anjoeka Pronk (TNO)	

WP (number and title)	WP8 Health Impact Assessment
Deliverable Number	D8.2
Deliverable Title	Report on the development of an exposome health impact model for working-life health, including specific health metrics, and application to intervention scenarios
Due date	February 2025
Actual date	February 2025
Dissemination Level	○ PU: Public ○ PP: restricted to other programme participants (within the Commission Services) ○ RE: Restricted to a group defined by the consortium (including the Commission Services) X CO: confidential, only for members of the consortium (including the Commission Services)

Lead beneficiary	UNIMAN	
Responsible author	Matthew Gittins	
E-mail / phone responsible author	matthew.gittins@manchester.ac.uk	
Co-authors	Roberto Carrasco	UNIMAN
	Luke Munford	UNIMAN
	Ioannis Basinas	UNIMAN
	Martie van Tongeren	UNIMAN

Contents

List of Tables

List of Figures

Glossary

AM	Arithmetic Mean
EC	Elemental Carbon
DF	Diesel Fumes
GM	Geometric Mean
GSD	Geometric Standard Deviation
Inc	Incidence
IR	Incidence Rates
Int	Intervention
MEL	Maximum Exposure Limit
ONS	Office of National Statistics
Pys	Person-years
RCS	Respirable Crystaline Silica
RR	Relative Risk
SD	Standard Deviation
Smk	Smoking
5-dec	5 year half-life decay in the risk of exposure
15-dec	15 year half-life decay in the risk of exposure
30%ave	30% reduction in the average exposure experienced
50%ave	50% reduction in the average exposure experienced
75%ave	75% reduction in the average exposure experienced
75max year	Max Exposure Limit set at the 75^{th} Percentile for the intervention
50max year	Max Exposure Limit set at the 50^{th} Percentile for the intervention
25max year	Max Exposure Limit set at the 25^{th} Percentile for the intervention

Brief Background/Introduction

Exposures at the workplace contribute to many non-communicable diseases (NCDs) with a similar magnitude as urban air pollution or obesity. Given the associated societal and economic (2-6% GDP) pressure, ensuring a healthy work environment is a strategic goal for the European Commission. Demographic changes (aging workforce, female workers) and the rapidly changing nature of work with respect to secure employment and migration, are posing additional challenges. We define the working-life exposome as all occupational and related non-occupational factors (general and socio-economic environment, lifestyle, behaviour). Taking a working-life exposome approach will help address these challenges by providing better insights in how complex working-life exposures are related to NCDs, for vulnerable groups (female, migrant, insecure job workers) or life stages. The working-life exposome is in its infancy and new approaches and methods are needed. In EPHOR a consortium of exposure, health and data scientists and technology developers will develop a working-life exposome toolbox, with stakeholder involvement. The toolbox will make available to scientists, policy makers and occupational health practitioners: 1) innovative methods for collection, storage, and interpretation of more complete and individual level working life exposome data; 2) better knowledge on how the working life exposome relates to NCDs, including complex interactions, vulnerability, biological pathways and early signs of health damage, by uniquely combining large-scale pooling of existing cohorts with focused case studies; 3) models for assessing the economic and societal impact of working life exposures. EPHOR will lay the groundwork for evidence-based and cost-effective preventive actions to reduce the burden of NCDs as a result of the working-life exposome. Thereby, health, wellbeing and productivity of the EU population will be improved and the burden on the EU health care systems reduced. EPHOR is part of the European Human Exposome Network comprised of 9 projects selected from this same call.

Aims/Objectives

Original Objectives - WP8

WP8 focusses on the development of health and economic impact assessment of working life exposome data that will provide knowledge on complex interactions and disease mechanisms. WP8 will use cohort data from WP5 and exposure prevalence from the application of the dynamic EuroJEM from WP2 for simulations during method development and the results of WP5, 6 & 7 for demonstration of the methods.

The objective is to bring the exposome concept to health impact assessment by developing methods to incorporate life course and co-exposures to multiple risks. Specific objectives are:

- Incorporate the working-life exposome concept into the models currently used to determine health impact (T 8.1, 8.2)
- Incorporate new knowledge obtained during the EPHOR project to estimate health impact for several hypothetical health-based interventions in the workplace (T8.3)
- Develop guidelines for health impact assessment to be included in the toolbox (T8.4)

OBJECTIVE/AIMS – Specific Work Package 8.3

The original work package 8.3 objectives were:

Task 8.3 - Exposome health impact assessment
A simulated longitudinal population cohort will be developed based on empirical data from WP2 and WP5 to estimate the impact of workplace interventions. The exposure(s), demographic and socioeconomic profiles of the simulated datasets cohorts will be based on data from WP2 and WP5 and information obtained from the wide range of published literature.

The conceptual model(s) developed in Task 8.1 will be used to implement initially relatively simple exposure scenarios and risk functions, evolving into more complex exposome profiles with various correlation structures and risk functions, involving multiple exposures and confounders, such as socioeconomic status as well as interactions between the risk factors. In particular, correlations between exposures and socioeconomic factors in relation to disease outcomes will be studied. A set of intervention scenarios will be developed, aimed to reduce future health burden and calculate the expected health impacts over a 20-60 year time period, accounting for regional and population differences. Scenarios will be developed with the benefit of stakeholder consultations organised in collaboration with WP10. Such scenarios would also look at changing exposures and risks over the life course, extending the working age, precarious work (e.g. people who do multiple temporary jobs), migratory work, etc. In addition to estimating the impact of interventions on clinical health outcomes, models will be developed for impact assessment using intermediate markers of exposure and incorporating concepts from the adverse outcome pathways. Such approaches would enable combination of health impact modelling with quantitative or qualitative evaluations of interventions, in relation to external exposures. This work will build on the mechanistic biological pathway modelling developed in T6.3 and T7.4. Task 8.3 will inform the development of guidelines in Task 8.4, in particular providing guidance on when the inclusion of complex exposure scenarios will result in more accurate estimates of burden of disease/health impact (and when conventional impact assessment models suffice).

These were summarised into the following. A simulated longitudinal population dynamic cohort will be developed. The exposure, demographic and socioeconomic profiles of the simulated datasets will be based on information obtained from the literature and expert internal and external opinion.

The objectives are split into two main tasks

1) To better understand how a single exposure-outcome relationship is influenced by changes in the individuals exposome. Here we simulate a known 'single' exposure – outcome relationship and then manipulate characteristics assumed to be representative of the persons exposome.
2) To better understand how the consequences of an exposure intervention can be influenced by differences in the exposome. We introduce a set of exposure interventions with differing characteristics, whilst manipulating both characteristics of the exposome and characteristics of the intervention.

Using simulated data, we hope to gain insight under a variety of exposome scenarios into the behaviour of an intervention on population level outcomes. Scenarios that we can manipulate without the interference of unknown factors. We aim for this work to be applicable to more than just one

workplace scenario but representative of real-world events, with estimates and conclusions of a representative true effect. These scenarios are based on conceptional models developed in WP8.1, the review of Working Life Expectancy developed in WP8.2, and real-world empirical studies outlining work related exposures that affect work and health. In order to be informative and grounded in a real-world scenario, the simulation will be based on studies of an exposure-outcome relationship associated with the construction industry, specifically Respirable Crystalline Silica (RCS) and Lung Cancer incidence. These will help inform the underlying structure and characteristics of our simulated data. Defining our 'known truths' the definitions of exposure levels experienced by simulated construction workers and 'true' effect of exposure on outcome.

Methods

The following outlines the methods used to develop a simulated longitudinal dynamic cohort that can be used to understand the influence of workplace 'exposure' interventions on a health outcome under varying exposome and intervention characteristics. Background for the decisions made within here came from reviews of the literature, and consultation with experts from within EPHOR and externally. To review the literature a summary has been provided within the Appendix.

Simulation Study

The following outlines our predefined definitions and methodology to simulate data representative of the construction industry, its exposome, and health outcome lung cancer incidence. The aim is to represent a hypothetically true working life exposome-outcome relationship. We then simulate an exposure/exposome intervention and its subsequent influence on the health outcome. We begin by defining the health outcomes of interest. Then describe standard methodology used to simulate the an event (i.e. lung cancer diagnosis), before modifying the methodology in order to simulate its when diagnosis occurred in the individual (e.g. at 65 years of age). We outline our definitions of the 'working life exposure' and 'non-exposure' related factors, their interrelationship (our hypothetical exposome), and their relationship to our predefined outcome. This may include single or multiple exposures along with key confounding factors, and the health outcome of interest based in the conceptual model. Finally, we will describe the proposed exposure intervention(s) in terms of its size and scope.

Study Population

We aim to simulate a longitudinal cohort study representative of the risk of an exposome-outcome relationship, such that study participants (construction workers) are continuously dynamically entering the cohort (entry to construction workforce) and leaving the cohort (at retirement, lung cancer, or death). This simulated population aims to be representative of construction industry employees who are at increased risk of Lung Cancer (LC) due to exposure to Respirable Crystalline Silica (RCS) and common co-exposures. The 'dynamic' cohort of simulated participants consistently replaced as they exit, will allow us to view how an intervention influences population-based statistics such as trends in new cases. To facilitate this, the dynamic cohort will represent a 100 year period between 1960 through to 2060. Any characteristics such as exposures, that contain a calendar time trend component, the time trend will be assumed to continue until 2020 at which point it is assumed to remain constant unless affected by an intervention.

Simulating the Outcome of Interest

Primary Outcome – Presence of Lung Cancer

The initiation of a new lung cancer diagnosis will be the simulated outcome event of interest for each individual within our cohort. Lung cancer is the second most common cancer in men and women. Cancer Research UK indicates a life-time risk of developing Lung cancer within the general population is estimated to be 1 in 13 for men and 1 in 15 for women.[1] It is rare for lung cancer to be diagnosed in those younger than 40, with the average age of diagnosis being in the mid to late 60s.

Simulating Lung Cancer Diagnosis

For each simulated data set, we will generate a binary outcome variable (Y) to represent presence of lung cancer (yes/no) using a Bernoulli distribution

$$Y_i \sim Bernoulli(p_i).$$

Where p_i based on the inverse of the logistic function, and represents the i^{th} simulated individual's probability of experiencing lung cancer diagnosis, given our known work-life exposure histories. The logistic function contains a predetermined vector of explanatory covariates $\beta' x$ and β_0 where β_0 defines the baseline pi or risk associated with an outcome when the explanatory characteristics are not present.

$$p_{it} = \frac{\exp(\beta_0 + \beta' x)}{1 + \exp(\beta_0 + \beta' x)}$$

Baseline Risk Defining β_0

To achieve a representative underlying risk function for LC we initially set the baseline risk to be associated with exposures set to zero during the working and post working life, i.e. never exposed to workplace exposures and never smoked. As limited information on risk of LC is available in construction workers, we have attempted to use estimates of lung cancer risk in a male, non-smokers, from the general population. Data from ECIS - European Cancer Information System (https://ecis.jrc.ec.europa.eu/) – for 2020 indicates a cumulative life time risk for lung cancer in the general population for both sexes and all ages across 27 EU countries ranging 5.2 % (Portugal) and 10.8% (Ireland). Overall risk was 7.2% with males at 10.7% and females at 4.6%. Cumulative risk for ages 25 to 40 years old was <0.1% for both sexes, and for ages ranging 40 to 75 it was 3.9%. Bruder et al showed lifetime risk of lung cancer in men and women in the Swiss population,[2] decreased in men from 7.1% to 6.7% between 1995 and 2013 (with some increase to a maximum of 7.3% in 1999–2003) while it increased among women from 2.5% to 4.1%, between 1995 and 1998 and 2009–2013, respectively. Similarly Cancer Research UK (www.cancerresearchuk.org) estimates lifetime risk of being diagnosed with lung cancer in UK as 8% for males, and 7% for females born after 1960 in the UK.[3] Age specific incidence rates for lung cancer male and female in the UK general population are reported in Table 1, as reported by the Office of National Statistics in the UK for 2017.[4]

Table 1 - Age Specific Lung cancer incidence rates per 100,000 persons in UK (2016-2018)[4]

ICD-10 code Site description Sex	C33-C34 Malignant neoplasm of trachea, bronchs and lung Males	C33-C34 Malignant neoplasm of trachea, bronchs and lung Females
Directly age-standardised rate	86.9	67.0
All ages	74.0	66.0
Under 1		
1-4		
5-9		
10-14		
15-19	0.2	
20-24		0.4
25-29	0.7	0.4
30-34	1.0	0.9
35-39	2.1	1.4
40-44	5.3	4.8
45-49	14.3	14.0
50-54	33.5	30.4
55-59	67.1	65.6
60-64	134.0	121.0
65-69	227.6	189.7
70-74	311.6	262.7
75-79	448.9	324.1
80-84	474.5	314.7
85-89	513.9	326.1
90 and over	489.1	255.0

Lung Cancer and Non-smokers

Few studies have independently assessed time trends for never smokers, as longitudinal collection and reliability of smoking information from population-based registries have been limited. The World Health Organization reports the incidence of lung cancer in never-smokers as approximately 25% of all cases.[5] However, there is considerable variance in the reported proportions of lung cancer in never smokers (LCNS) ranging from 10% in males in Western world,[6] to 40% in females in Asia.[7] A UK based cohort study of 3.7 million people looked at lung cancer in non-smokers from 1998 to 2018. For women, the age-adjusted incidence rates in non-smokers were relatively stable over the past 20-years at around 1.5 per 10,000 person-years. The corresponding result for men was 1.83 for the same period of time. Between 1998 and 2008, age-adjusted incidence rates in men decreased by 9% per year on average and by 3% per year thereafter (from 2.1 to 0.8).[8] The UK Biobank with 218,892 never-smokers reported the incidence rate of lung cancer at 13·4 per 100,000 person-years (95% CI: 11·5–15·6), accounting for 13% of the total lung cancers in UK Biobank.[9] Further analysis of

UK biobank data has indicated that just 12% of lung cancer deaths in those over 40 were present in never smokers. This was slightly higher in those aged under 40-50 (19% though small lung cancer cases) and for females (15%) at time of death, but remained consistent across all age groups including within genders. Wakelee et al. using data from six big epidemiological studies found age-adjusted incidence rates of lung cancer among never smokers age between 40 to 79 years ranged from 14.4 to 20.8 per 100,000 person-years in women and 4.8 to 13.7 per 100,000 person-years in men.[10] A large cohort study of male construction workers in Sweden reported an increase in age-adjusted incidence rates of non-smoking-related lung cancer from 1.5 per 100,000 between 1976 to 1980 to 5.4 per 100,000 between 1991 to 1995.[11]

Definition of Baseline risk: *For this study we assumed the age specific baseline risk of lung cancer follows the incidence rates set out by cancer research uk (see Table 1) for males within the general population. These are currently based on the general population some of whom will have smoked and will have been exposed to LC risk factors. We therefore reduced the incidence rates to 10% (males) and 15% (females) of the value in order to ensure they are representative of the never smoked never exposed baseline risk.*

Explanatory `Exposure' Variables

The section defines the key explanatory variables used to simulate our lung cancer diagnosis. These will be based on the literature outlined in section 0, and will include characteristics and distributional properties of our exposome i.e. the individual exposures present in the multiple exposure concept. Starting with a single 'primary' exposure, we expand to multiple additional co-exposures. In addition to their distributional properties, we pre-define their known relationships with the outcome.

For the purpose of this analysis, we define occupational exposure as the concentration of the substance or agent in the breathing zone of the workers during the working day. The `cumulative exposure' is estimated as the annual average exposure in a job (in mg/m3) over the duration of the job (in years) summed for all jobs that the individual held within the period of interest (mg/m3 years):

$$Cumulative\ exp = \Sigma(T_i \times C_i)$$

where T_i is the period in years that a person worked in job *i*, and C_i is the average exposure intensity that they were exposed to while in this job. The average exposure is assumed change over time within the same job with intensity generally being reduced as year's progress. This annual decline is typically a result of improvements in technology, changes in legislation or the underlying processes within the job. Typical annual declines in occupational exposures are reported to be in the range of 1 to 10%, although instance of annual increases have also been reported for certain job/industry and substance combinations.[12] For each exposure variable, the estimated cumulative exposure will be included as a continuous covariate.

Defining Outcome Given Time Varying Exposure(s)

A key component of the study relates to the time of LC diagnosis. The LC diagnosis Y outcome defined in relation to the explanatory covariates X present in the logit function $\exp(\beta_0+\beta'x)$, is extended to time when LC diagnosis occurred based on increase in cumulative exposure across the lifetime.. For each year of exposure, the cumulative exposure covariate(s) are updated and the probability of a participant being a lung cancer case determined. If the participant is deemed to be a case, their status and cumulative exposure(s) is fixed. This continues until all subjects have been allocated as a lung cancer case and the year of diagnosis defined, or they reach their simulated age

of death. To incorporate this censoring, we simulate for each subject a life expectancy without lung cancer. Participants are assumed to be LC free if they are not diagnosed before their age of death. Using ONS life-tables the life expectancy for UK males born in 1980 was 71 years old, increased to 79 years old in 2019. We assigned age of death at random based on age specific death rates reported in life tables associated with those born between 1980-82 deemed suitable for those going through the intervention period.[13]

Definition: *Based on ONS lifetables we will simulate life expectancy per individual assuming a simplified but representative estimate population life expectancy.*

Defining the Covariate Exposure Histories

To simulated subject exposure histories, we generate a time-varying exposure profile for each simulated subject[14 15]. Exposure is then defined as e_t where t represents the year the participant was exposed i.e. $t = 1$ is the first year of working life. We simulate an annual exposure experienced per subject over their duration of exposure. The cumulative exposure is the summed exposure of the preceding years.

Defining Primary Exposure – Respirable Crystalline Silica (RCS)

Exposure to RCS in the construction industry is the primary working life exposure of interest.

Defining the Exposure Structure

Occupational exposures are commonly measured on a daily, full-shift (i.e. 8-hr) basis and used to develop exposure metrics that may be biologically relevant to the health outcome of interest. For chronic diseases including cancers cumulative annual exposure during the duration of employment is commonly used. The average exposures for RCS follows a non-negative geometric distribution. The cumulative annual exposure is typically calculated using the arithmetic means of the daily average per year for a particular role, aggregated over the duration of employment in the role. To simulate this under varying exposure histories we need to understand the annual average exposure experienced, the variation within and between individuals, and its corresponding effect on outcome.

Background RCS

The current EU Directive on Carcinogens and Mutagens at Work implemented recommended a limit of 0.1 mg/m^3 exposure to RCS dust.[16] Exposure to RCS during construction work is reported to differ depending on the period of interest with in principle levels of exposure being much lower in recent years primarily as result of changes in technology, legislation and exposure controls. For example, Dutch construction workers in 2011 were reported to be exposed to RCS levels with a Geometric Mean (GM) level of 0.1 mg/m^3 and a Geometric standard deviation (GSD) of 3.84.[17] In addition, RCS levels in construction have been reported to decline by approximately 6 to 10% on an annual basis and current (GM) levels of RCS exposure among Danish construction workers were reported to be much lower ranging between 0.005 and 0.018 mg/m^3 with an overall cross industry GM close to 0.014 mg/m^3 and a GSD of around 3.51.[12 18 19] Although that the average exposures across the industry appear to be low considerable differences between occupations exists. Earlier research characterising the variability of RCS exposure among construction workers reported the between workers variance component to be 3 folds larger than the within workers variance components (3.2 vs 1.0), which corresponds to a 3 orders of a magnitude variation in the measured exposure levels between workers – i.e. a ratio between the 97.5 and 2.5 percentiles of the distribution of the log-transformed corresponding variance component equal to 1,100.[20 21]

Determining our Exposure Characteristics (Annual average, within vs between person variation)

Our exposure estimations are based on daily measurements among Danish construction workers in 2018.[17] In order to define average annual exposure levels for 5 years interval periods across the dynamic period from 1960 until 2020, we assume exposure that since 1970 exposure declines every 5 years by 6%. To avoid using unrealistic estimates amid a general lack of personal measurements for RCS prior to 1970s[22] we assume the average levels of exposure between 1960 and 1970 remained constant and equivalent to those encountered in the first period of the 1970s. These derived exposure estimates (

Table 2) are the based on sample averages of daily measurements and are reported in terms of the Geometric Mean. Based on these daily measurements we estimated the within-person (day-to-day, within a year) and between person geometric standard deviations to be 2.8 and 4.5, respectively.

To determine the average annual exposures, and between and within person variation in the annual average exposure among a population of construction workers, we performed a smaller initial simulation study. Full details can be found in the appendix, but, for 100,000 individuals (n=1000, reps=1000) we randomly allocated a start year between 1960 and 2020, and a retirement year at age 65. We then simulated the daily exposures experienced, assuming the above characteristics on average daily values and within and between variation in daily measure. We then calculated the individual mean exposure per year, before summarising the average of the annual estimates across the sample. We also calculated the between and within person variation (year-to-year) in the annual average exposure across the sample. These are described in Table 3, and the within and between person variation in annual average of daily exposure was, 1.2 and 4.5.

Table 2 - Estimated average Geometric mean daily levels of RCS exposure from 1960 to 2020 in the construction industry. Estimates are based on the results of Boudigaard et al. assuming a 6% annual decline in exposure following the year 1970.

Time period	Start year	Stop year	Average GM RCS level (mg/m^3) based on daily measurements	Average AM RCS (mg/m3) based on annual average of daily exposure across the population
1	1960	1965	0.238	0.404
2	1965	1970	0.238	0.404
3	1970	1975	0.238	0.404
4	1975	1980	0.174	0.296
5	1980	1985	0.128	0.218
6	1985	1990	0.942	0.161
7	1990	1995	0.069	0.118
8	1995	2000	0.051	0.087
9	2000	2005	0.037	0.063
10	2005	2010	0.027	0.046
11	2010	2015	0.020	0.034
12	2015	2020+	0.015	0.025

Exposure - Response effect – our pre-defined 'known truth'

Here we can define the exposure-outcome effect i.e. our 'known truth'. We will define our `known truth' such that a small, medium, and large exposure effects are present. This will give us insight into

how changes in the exposome influence the intervention effect over a varying magnitude of increased risk.

As outlined in section 0 typical hazard ratios for studies investigating cumulative RCS exposure have ranged between 1.02 and 1.40 (based on 95% C.I.s) per 1 mg/m^3 year unit increase in total cumulative RCS exposure. These sizes of effects are also confirmed by a recent meta-analysis, which assessed the exposure-response relationship between occupational RCS exposure and lung cancer among nineteen studies published between 1991 and 2020.[23] Study estimates were grouped and analysed according to six levels of average annual RCS exposure: ≤ 0.49 mg/m^3, 0.50–0.99 mg/m^3, 1.00–1.99 mg/m^3, 2.00–2.99 mg/m^3, 3.00–3.99 mg/m^3, ≥ 4.00 mg/m^3 using random effect models. Linear and cubic splines were also implemented to study further the exposure response relationship. The results of the categorised analysis suggested a clear positive exposure response relationship with a pooled risk estimate of 1.27 (95% CI=1.19-1.36) whereas the results of the splines were similar suggesting a linear positive trend with a 25% increase per cumulative unit of exposure (RR of 1.25, 95% CI = 1.03-1.49).

Final Definition RCS: Assume an average annual exposure starts at 0.404 mg/m^3 in the 1960-65[19] under a truncated log-normal distribution will be simulate RCS exposure for 1970 with a 6% decline per decade after until 2020 after which it is held constant. We expect that the ranking of the individual's RCS exposure remains similar over time, so that individuals with high exposure will continue to have relatively high exposures throughout their exposure period (i.e. working life). Using the variance distributions reported in the Dutch[17] and Danish[19] studies and our min simulation study reported above we can calculate the between and within person variation as GSDs of 1.2 and 4.5, respectively. This results in an approximate within person correlation for the annual average of approximately 0.21. The pre-defined relative risk associated with an increase of 1 mg/m^3 in cumulative exposure will be defined assuming a range of small, medium and large increases in risk to be **2%, 5%, and 25%.** This will provide insight into the intervention effect under differing underlying risk scenarios.

Lagged Exposure–Response – 'Decaying' Risk and Latency Periods

Decaying Risk

Subjects with the same cumulative exposure but differing temporal exposure patterns can be associated with differing disease risks. For example, exposure on any year may increase your risk of LC for the rest of your life equally (irrespective of the time since this exposure occurred); alternatively, the risk for developing LC as a result of the exposure may reduce with increasing time since the exposure occurred (called decaying risk). To simulate a decaying risk for cumulative exposure, we can modify the covariates representing the annual exposure history associated with lagged decaying effect preceding each year t.

$$e_l = e_{(t-l)} * 2^{(-l/d)}$$

where e_l = decay-adjusted annual exposure associated with l^{th} year prior to the current exposure year t, $e_{(t-l)}$ = original annual exposure occurring at year t-l, d = decay half-life in years. For the purposes of the simulation study we will simulate life time decaying risk prior to t, and will explore the influence of a decaying risk under **no decay** (i.e. exposure risk does not reduce over time) **a 5 year, and a 15 year half-life decay**.

Latency Period

Occupational exposures commonly associated with ill-health events, particularly cancer, often contain latency periods i.e. a delay between exposure and disease development. Minimum latency periods of 5 or 10 years are thought common depending on the cancer of interest, with solid state cancers such as LC thought to have a max latency period between up to 50 years.[24] We define a period of delay for each individual where exposed sees no directly related increase in risk (i.e. exposure remains zero), before the increase in risk occurs. For a cumulative total exposure the lagged annual exposures during the latency period is set at zero, before increasing at the level observed at the beginning of the lag period.

$$e_l = 0 \text{ if } l <= t_l$$

$$e_l = e_{(t-l)} \text{ if } l > t_l$$

Where annual exposure for each t years is e_t, e_l is the annual exposure that occurred in the previous l^{th} year, and t_l is the length of the latency period. For the purposes of the simulation study the latency period will assume a truncated log normal distribution with a mean of 35 years, and a s.d will be calculated as the range of latency period divided by 6.

$$ln(s.d) = [ln(max) - ln\ (min)]/6$$

Definition: The range of latency periods to be applied are defined as **10-50 years each with a GM 35**.

Co-Exposure(s) Definition – The Exposome

A persons exposome encompasses a set of interrelating exposures experienced during a person's working and non-working life that are thought to modify their risk of a health event. Here in a construction working life exposome, this relates to any set of common chemical or other hazardous exposures present on a construction site such as asbestos, diesel engine and other combustion fumes, and direct or passive smoking. These co-exposures commonly occur in construction and may co-exist with our proposed main exposure RCS in that they are often produced under similar processes and so thought to be correlated. To explore the influence of working life co-exposures we propose to focus on simulating additional diesel engine exhaust fumes, and smoking as an additional set of chemical exposures.

The Co-exposure: Diesel Fumes

A secondary co-exposure `diesel fumes' will be simulated under the same processes described for the main exposure. We provide a summary of the literature within the appendix. We assume the same time trends in exposure (i.e. 6% decrease in exposure levels per year) are also applied and a cumulative total exposure over their working life generated. In terms participants exposure duration, if subjects are exposed to the primary exposure 'RCS then we consider them to also be (potentially) exposed to our secondary exposure diesel fumes. Based on the above assumptions estimates of average GM levels reported in the Dutch[40] and Danish[39] studies, Table 3 below reports the GM per 5 years intervals.

Table 3 - Estimated average Geometric and Arithmetic mean levels of daily diesel exhaust exposure from 1960 to 2020 in the construction industry. Estimates are based on the results of Ziembicki et al [25] assuming a 6% annual decline in exposure following the year 1970.

Time period	start year	stop year	Average GM EC level (ug/m^3)	Average AM EC level (ug/m^3)
1	1960	1965	15.308	23.269
2	1965	1970	15.308	23.269
3	1970	1975	15.308	23.269
4	1975	1980	13.145	20.000
5	1980	1985	11.288	17.181
6	1985	1990	9.694	14.759
7	1990	1995	8.324	12.677
8	1995	2000	7.148	10.891
9	2000	2005	6.138	9.355
10	2005	2010	5.271	8.035
11	2010	2015	4.526	6.902
12	2015	2020+	3.887	5.929

Within vs Between Person Variation

Representative data on the distribution of variance components for diesel exposure in the construction industry is not available. Using the variance components distributions available in the Dutch[40] and Danish[39] studies for RCS and the GSD of 3.32 from the earlier mentioned study among Canadian construction workers[64] we can estimate a range of GSD values for between and within persons variance of 2.77-2.85 (so adopt 2.8) and 1.79-1.2.06 (so adopt 1.90), respectively. As with the RCS these are associated with the variation in the daily values. Based therefore on the simulation study described above, the within and between person GSDs were then estimated to be 1.1 and 2.8. This results in an approximate within person correlation in the annual average of 0.28 for the annual average.

Final Definition Diesel: Assuming an average (Arithmetic Mean) annual exposure starts at 23.269 ug/m^3 in the 1970s with and between-person geometric standard deviations for annual average exposure of 1.1 and 2.8, respectively. [26] We simulated a set of exposure estimates based on a truncated log-normal distribution starting in 1970 with a 6% decline per year until 2020 at which point it is held constant. The pre-defined relative risk associated with an increase of 1 ug/m^3 will be set at 1.0005.This is based on Vermeulen et al. in a meta-regression analysis of three large occupational cohort studies estimated an ln(RR) of 0.00098 (95% CI: 0.00055, 0.0014) for lung cancer mortality with each 1-µg/m3-year increase in cumulative EC exposure.[27] There is currently no evidence of a decay function, and latency period appears to be approximately 10 years. We will maintain these throughout our simulations. As with RCS and smoking we also assume that the ranking of individual annual average diesel exposures remains largely similar over time.

Smoking

Smoking is a significant risk factor for lung cancer, being associated with smoking since the early 1950s and now widely agreed to be a causal in relationship. For background information on the definitions of smoking we have produced a summary of the literature which can be found in the appendix.

Final Definitions of Smoking: We assume 60% of our construction population aged between 16-30 begin smoking in our 1970s cohort. This then decreases by 5% per decade in line with general population trends. We randomly assign a smoking initiation age and duration using a truncated normal distribution with a mean age 22 years (s.d 5 years, min age 14), and mean duration 30 years (s.d. 10). We simulate the average number of cigarettes per day in those that smoke to be 18.5 in the 1970s also decreasing by 1 cigarette per decade until its 14.5 in 2010s at which point it is held constant. We assume smoking habits remain largely similar over time with high frequency smokers remaining high frequency smokers throughout their exposure period. We assume a between person variation with s.d. of 5 cigarettes per day, and a within person variation of s.d. = 2 cigarettes per year in terms of the average cigarettes per week. This results in an approximate within person correlation of 0.7. Smoking latency is randomly assigned but matches the characteristics of RCS, i.e. fixed at a minimum of 10 years (max 50 and GM=35). Decaying risk here is based on the SYNERGY study analysed in work package 8.1, and set to be a 10 year half-life decay. The associated relative risk for a 1 unit increase in pack-years will initially also follow the results from the SYNERGY study at 1.12 i.e. a 12% increase risk per additional pack-year. However, smoking is a key component of lung cancer risk, an so we will modify the cumulative pack years RR, in order to retrofit the influence of smoking such that number of lung cancer cases and the distribution of lung cancer cases matches approximate the general population as recorded by Cancer Research UK.

Correlation Structure between Work-related Exposures

Work-related exposures such as RCS, diesel engine exhaust fumes, and smoking are likely to have a complex correlation structure. Strong correlations may influence the incidence rates of new LC cases, and any effect of an intervention that might have been implemented. To better understand the influence of correlated multiple exposures we introduce the additional exposures alongside RCS, with increasing strength of correlation. We begin by introducing the multiple exposure with an independent relationship (i.e. correlation set at 0 for all three exposures), before increasing the correlation between exposures to 0.5 i.e. a high strength correlation for all three exposures. In a third correlation structure we include a bespoke mix of correlations between the multiple exposures will be fitted, see Table 4. These correlations proposed attempt to represent a high correlation in the working only exposures (RCS & Diesel Fumes) where as a lower correlation is present with the non-working only life exposure (i.e. smoking), these are outlined in Table 4. These are thought to better reflect real life exposures.

Table 4 – Correlation Structure of Work-related Co-exposures

Model		Working Life Exposures		
		RCS	Diesel	Smoking
Multiple Co-exposures	RCS	1		
	Diesel fumes/Diesel	0	1	
	Smoking	0	0	1
	RCS	1		
	Diesel fumes/Diesel	0.5	1	
	Smoking	0.5	0.5	1
Bespoke Structure	RCS	1		
	Diesel fumes/Diesel	0.5	1	
	Smoking	0.1	0.1	1

Additional Non-working Only Life Factors

In addition to smoking, we seek to include some 'non-work-related confounding' factors present in the exposome concept. These are factors related to an increased risk and differential exposure that are not directly related to work but are more common in a particular industry/job. These include age, gender and represent differences in individuals that are fixed over their lifetime. One advantage of a simulation study is that we can compare directly the intervention effect in the same subject with and without the exposure effect (i.e. the counterfactual). This means confounding factors are fixed within the same subjects as only the exposure is modified. Therefore inclusion of these factors will have no effect on the intervention and instead we aimed aiming to produce simulated cohorts of individuals that are generalisable and representative of target population, construction workers. We therefore defined:

Age at entry: Simulated subjects are all assumed to enter the workforce in their 20s with a truncated normal distribution (min age = 16, mean = 20, sd =3). We assume that age at entry itself has no influence on the subject's lung cancer risk outside of that defined by the baseline risk or their exposure profile.

Gender: The percentage of females in the construction industry as reported by the Office of National Statistics has been consistent since the 1990s at ~10%.[28] The majority are thought to hold office jobs meaning daily RCS/Diesel exposure on a construction site would be low. Details on female construction workers exposure is limited. To account for this disparity, we have assumed the average exposure to RCS/Diesel is 80% lower than for the male workers. With respect to smoking, the proportion of female smokers since 1970s approximately matches the general population, however average number of cigarettes per day is ~4 lower than for men. We therefore maintain the proportion of smokers in both genders but reduce the number of cigarettes per day by four per decade for females.[29] Cancer Research UK indicates that between 2016-18 the current age standardised lung cancer rates for females were 70.1 and males 90.6 per 100,000.[30] However, in never smokers the relative risk of LC is 1.30 times greater in females. Given we are including smoking as a key exposure, we ensure this is consistent within our simulated construction cohort.

Exposure Intervention

Reducing or preventing work-related ill-health due to occupational related exposures is achieved through reduction or elimination of the exposure experienced by the employee. A recent systematic review of occupational intervention studies occurring between 1960 and 2019 and targeting exposure to chemical and biological agents,[31] classified interventions into one of four intervention types:

- A control measure such as a ventilation system,
- behaviour/education/training program,
- policy e.g. smoking ban or limits on exposure,
- or Personal Protective Equipment (PPE).

The majority of the studies reviewed (73%) reported an intervention outcome effect related to a reduction in the exposure. These influences were observed to vary between 5/6% for educational programs, to 30% for control measures, to 80% policy interventions specifically bans. Though this was also observed to vary with characteristics of the population and intervention understudy. Not all interventions are direct interventions on a specific work force, rather public policy changes that may or may not have a positive effect on work force health. For example, government policies such as those relating to national retirement age, particularly extending it, may also be considered as an intervention one that indirectly affects employee risk.

To better understand the influence of potential interventions on exposure and their risk of lung cancer outcome. To do so, within each simulation scenario outlined we will simulate an exposure intervention based on the intervention scenarios outlined above. These are defined as the following set of intervention scenarios:

- The annual exposure level is reduced e.g. by 30%.
- The maximum value of the annual exposure level is reduced e.g. by 1/3rd (i.e. simulating imposed limits)
- An extension of the retirement age, currently set to 65, extended to 68.

The first two interventions will be repeated such that:

1) for the primary exposure 'RCS' only i.e. that the intervention does not also influence the secondary working life exposures,
2) and for all working exposures i.e. both the primary (RCS) and secondary exposure (diesel) are similarly reduced.

When applying each intervention we simulate that they occur in all participants within the cohort, and that each occurs at a specific calendar time point. This simulates the implementation of an intervention within a population, such as a new policy applied to a workforce where some have already been exposed. Using our Birth Cohorts as a guide (1960+) we set the intervention to occur in the year 2010, this gives a 10 year period post our intervention (until 2020) where we have some understanding of the exposures and trends in exposures. After 2020 the previous downward trends in exposures are stopped and the exposure levels are held constant. The only change is then due to the intervention effect.

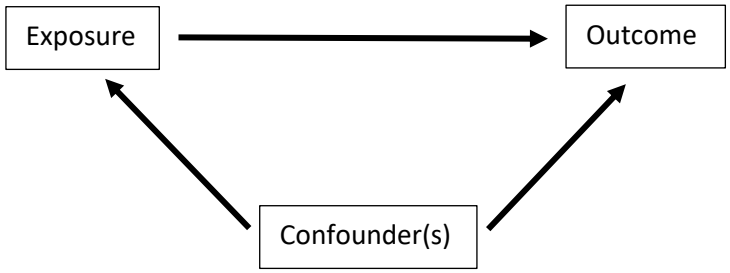
Developing the Exposome-outcome framework

The following outlines our planned progression of increasingly complex exposome scenarios. We plan to increase complexity in our exposome from a simple exposure-outcome model to the multi-exposure, multi-characteristics - outcome model. To describe these increasingly complex relationships we employ the graphical tool to represent the hypothetical causal relationships, a directed acyclic graphs (DAGs).[32 33] A concept that has been developed to help describe casual relationships, understanding confounders, and potential sources of bias in exposure–outcome relationships.[32] In a DAG, a causal relationship is represented by an arrow, or path, between the variables, illustrating the direction of cause to effect. Within each of the scenarios proposed explore the influence of a set of health interventions (see Section 0) on the proposed health outcome (see Section 0) under the changing exposome characteristics.

The Basic Single Exposure-outcome Model

We first look to confirm that a) our simulations are accurately portraying the single exposure – outcome relationship, b) that we understand how the underlying exposure characteristic can influence our proposed health outcome. We begin by developing the single exposome-outcome relationship where the single exposure is Smoking. This allows us to confirm the underling incidence rates match the general population. Occupational exposure assessments are observational in nature with significant amounts of confounding, as we are comparing the counterfactual (i.e. within person comparison of the intervention effect). Therefore, confounding factors such as gender, and birth cohort effects are not impacting the intervention effect other than through generalisability of the results to the construction population. Figure 1 describes the base model of a single exposure outcome relationship for smoking and LC diagnosis.

Figure 1 – A DAG representing the basic model, single exposure single outcome relationship with additional confounding



Under the single smoking exposure – LC outcome model, we do not compare multiple scenarios, only ensure that our LC incidence rates match approximately the general UK population as described by Cancer Research UK.

Introduction of additional time-varying co-exposures (independent)

Under the exposome concept, the employee is assumed to experience multiple interrelating exposures during their working life, some directly work related and some not directly related to work but common such as smoking. These additional exposures (see Figure 2), including the primary

'RCS' exposure are time-varying with a complex set of interrelationships. Here we incorporate two additional co-exposures to the already included smoking; the main RCS and diesel fumes. As with smoking, RCS and Diesel fumes are the time-varying cumulative dose received during their working life. We begin by including one co-exposure at a time, starting with RCS and then repeat with diesel. Initially, we assume each time-varying exposure is independent of each other, i.e. a high RCS exposure does not necessarily indicate a high diesel fumes exposure as well (as described in Figure 2).

Figure 2 – A DAG representing the multi-independent exposure(s) - outcome relationship with additional confounding

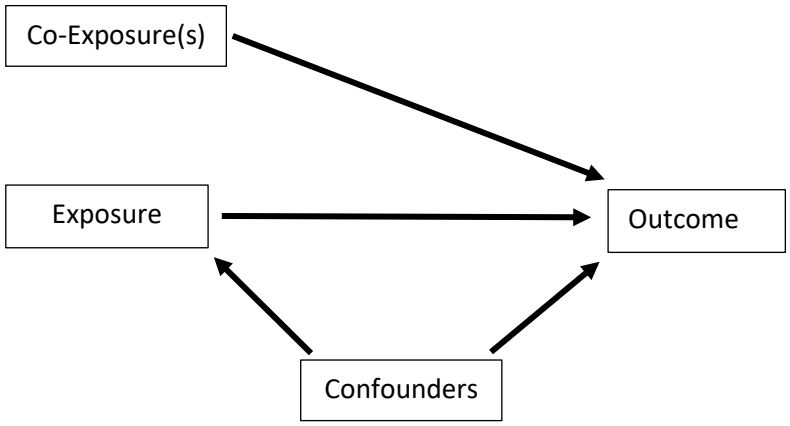


Table 5, outlines the scenarios we have investigated under the addition of the main exposure 'RCS' only. We simulated adjusting the effect size associated with a unit increase in cumulative exposure and the decaying risk function, applied such that there is a half-life of 5 and 15 years.

Table 5 - Scenarios to be simulated for Single Time-Varying Exposure (Fixed Work Duration)

Exposure(s)	Scenario No.	RCS Effect Size 'known truth'			Risk Decay Half Life	
		0.02	5%	25%	5yr	15yrs
Smoking + RCS	1.001	X				
	1.002		X			
	1.003			X		
	1.004	X			X	
	1.005	X				X
	1.006		X		X	
	1.007		X			X
	1.008			X	X	
	1.009			X		X
Smoking + RCS + Diesel Fumes	2.001	X				
	2.002		X			
	2.003			X		
	2.004	X			X	
	2.005	X				X
	2.006		X		X	
	2.007		X			X
	2.008			X	X	
	2.009			X		X

Introduction of co-exposures (with correlation structures)

Working life co-exposures are rarely thought to be independent (Figure 3). We repeat the simulated scenarios assuming co-exposures are correlated.

Figure 3 – A DAG representing the correlated exposure(s) - outcome relationship with additional confounding.

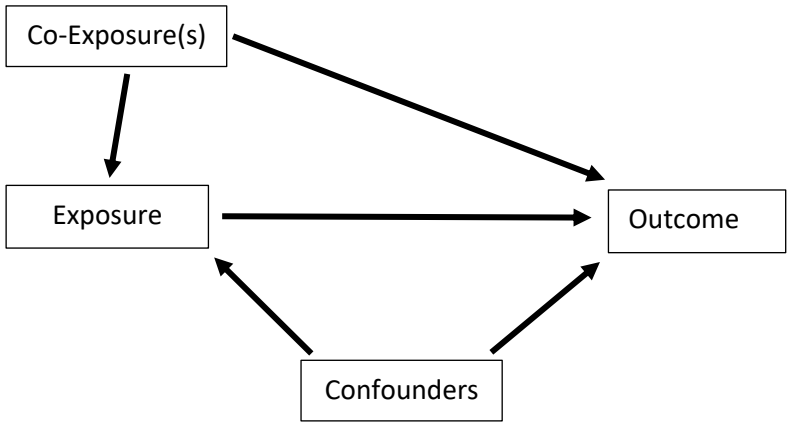


Table 6, repeats the simulations presented in Table 5 with co-exposures assumed to be strongly correlated (0.5) and under a bespoke correlation structure. See section 0 for more details.

Table 6 - Scenarios to be simulated for Single Exposure (Random Work Duration) with a single additional moderately correlated work exposure (Diesel fumes)

Exposure(s)	Scenario No.	RCS Effect Size 'known truth'			Risk Decay Half Life		Exposure Correlation Structure?	
		0.02	5%	25%	5yr	15yrs	Large=0.5	Bespoke
Smoking + RCS	3.001	X					X	
	3.002		X				X	
	3.003			X			X	
	3.004	X			X		X	
	3.005	X				X	X	
	3.006		X		X		X	
	3.007		X			X	X	
	3.008			X	X		X	
	3.009			X		X	X	
Smoking + RCS + Diesel Fumes	4.001	X					X	
	4.002		X				X	
	4.003			X			X	
	4.004	X			X		X	
	4.005	X				X	X	
	4.006		X		X		X	
	4.007		X			X	X	
	4.008			X	X		X	
	4.009			X		X	X	
Smoking + RCS	5.001	X						X
	5.002		X					X
	5.003			X				X
	5.004	X			X			X
	5.005	X				X		X
	5.006		X		X			X
	5.007		X			X		X
	5.008			X	X			X
	5.009			X		X		X
Smoking + RCS + Diesel Fumes	6.001	X						X
	6.002		X					X
	6.003			X				X
	6.004	X			X			X
	6.005	X				X		X
	6.006		X		X			X
	6.007		X			X		X
	6.008			X	X			X
	6.009			X		X		X

Analysis

Data Generation

To ensure the results of the simulation study performed here are 1) repeatable and 2) any errors can be checked, the series of random numbers used to generate each dataset are produced from a pseudo random number generator. Simulations are considered independent if using different starting seeds to generate datasets for each scenario.[34] The seed shall be predefined at the start of the simulation as the date of the first EPHOR project kick-off meeting on 28/01/2020, i.e. 28012020.

Estimating Impact of the Intervention

To understand the health intervention effect, we need to quantify the health impact with and without the intervention applied. To keep the simulation procedure simple and efficient, we propose to record and then compare with and without the intervention(s):

- Change in annual incidence rates in 10 year periods (i.e. Intervention year, 10, 20, 30, 40, 50 years post intervention).
- Relative Risk in lung cancer annual incidence rate. (10 year periods post intervention)
    - The average age of lung cancer diagnosis (per birth cohort decade)

Summarising Across the Simulations

The estimates for each i^{th} simulated dataset for each scenario are stored. The i^{th} estimates are reported as averages $\bar{\hat{\beta}}$. [35] The standard deviation of the i^{th} estimates represents the standard error $se(\hat{\beta})_{ave}$. and will be used to assess the performance with and without the interventions applied.

Sample Size & Simulation No.

Data is generated by producing random draws from a known parametric model (see section 0). The following outlines our definition of the within cohort sample size and the number of repeated simulations to provide a reliable result not related to random chance alone.

Sample Size of Simulated Datasets

In most simulation studies a sample size calculation for the number of simulations being performed is based on the bias associated with an exposure effect.[36] Here we are interested in determining if the health intervention is providing a significant change in the health of the population.

We would want, for example, to be able to confidently say that there is a change in the annual incidence rate of cases present if the intervention occurred vs not. Given we are comparing the same individuals under two different conditions, we performed a sample size calculation based on a paired sample proportion test assuming 5% significance and an 80% power. Based on our proposed definitions, and aim to reflect observed incidence rates for LC, we would expect the proportion of subjects with lung cancer prior to intervention in the construction industry to be approximately 0.0013 i.e. 130 per 100,000pys. If we define the minimum absolute difference in proportions to be 1% reduction i.e. 120 per 100,000pys, then we would require simulated samples of 1,962,213 individuals per year. To achieve this in a dynamic cohort of construction workers joining at uniform rate over the 100 years, we need approximately 5,000,000 individuals in total. This equates to for example 50,000 persons per repetition for 100 repetitions.

Results – Building the Exposome

The following describe the results of the simulation study outlined above.

Smoking Only (Base) Model

We first developed the baseline model containing baseline risk estimates, participant factors and smoking history only. The parameter estimates for cumulative smoking risk were back transformed such that the resulting LC risk was representative of the current UK general population i.e. annual incidence rates and life-time risk prior to workplace exposures being applied. Life-time risk i.e. the percentage of the general population that are diagnosed with LC during their lifetime is calculated from a 50,000 sample of simulated participants indicates a life-time risk for the entire study period (1960 to 2060) of approximately 5.1%. This period includes post 2020s where downward trends in exposure prior to and after 2020 contribute to lower life-time risk. In the cohort of individuals born prior to the 1980s only (i.e. the group currently contributing to empirical studies, the life-time risk is approximately 6.9% close to the 1 in 15 current estimates of general population life-time risk. Figure 4 then a LOWESS smooth plot of estimated annual LC incidence rates per 100,000 person-years, i.e. per 100,000 construction workers at the start of each year. Annual incidence rates (per 100,000 pys) in Figure 4 for the period 1990s to 2020s approximately match annual incidence rates reported for the general population between 120 in the late 1990s to 110 in the late 2010s. The gradual downward trends over this period are also representative. Note, prior to 1990s, the dynamic cohort was in the development phase made up of predominately younger individuals, with lower exposure, and early in the latency period for any exposure risk experienced. Hence the much lower incidence rates. Similarly post 2050, the cohort starts to age (as they are not replaced by younger individuals, hence the slight up-turn in incidence rates.

Figure 5, replicates the annual incidence rates for LC in Figure 4 but only includes the period of the study post 2010 when our simulated interventions are applied. We also include cumulative Working Years of Life Lost (WYLL), i.e. the period of work lost that would have been expected had they had not developed LC (if that occurred prior to pension age 65). Table 7, provides summary statistics for the period post the intervention year, this is reported in 10 year points and represents the 5 year average, 2 years pre and post the year of follow up. The table reports incidence rates, average age of diagnosis, and the average working years of life lost per year.

Figure 4 – Annual Incidence rate per 100,000 person years across the study period, Smoking only Model

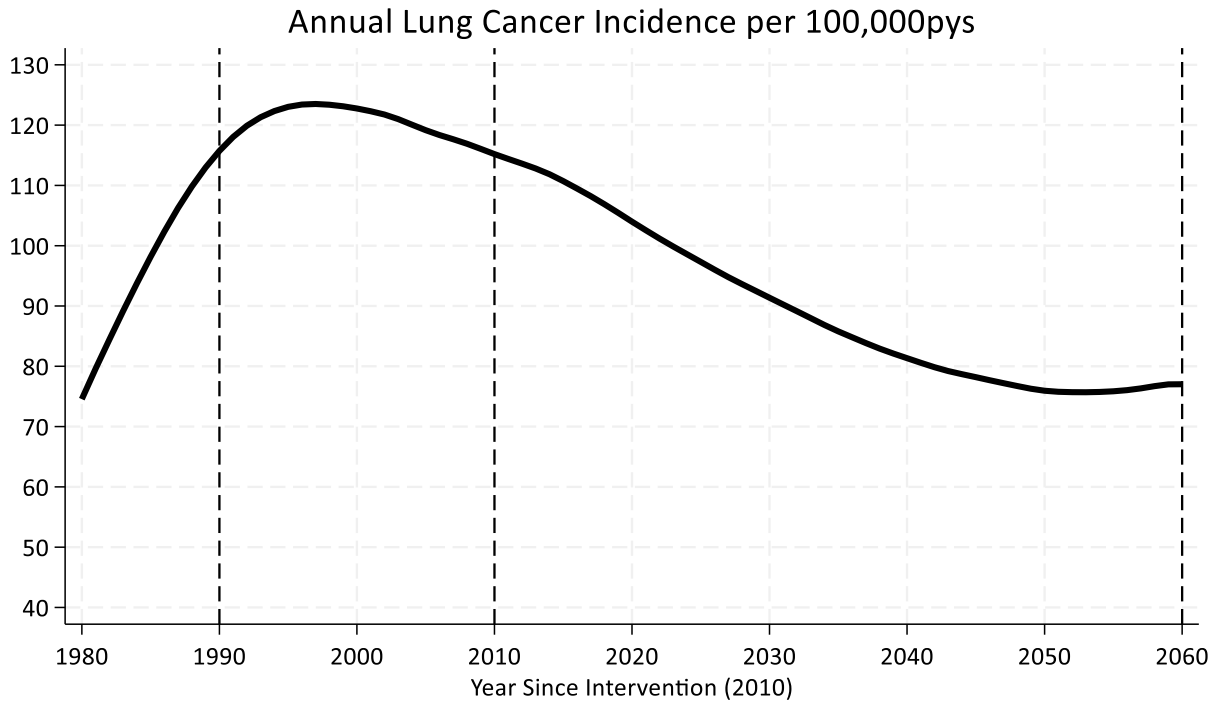


Figure 5 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) for smoking only model.

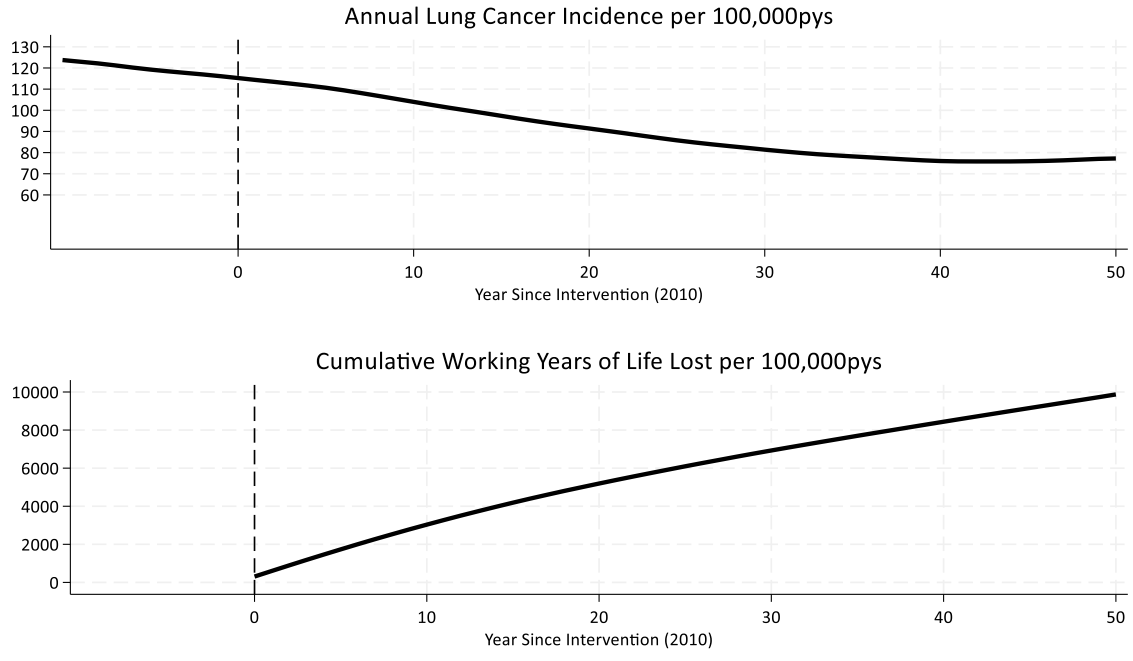


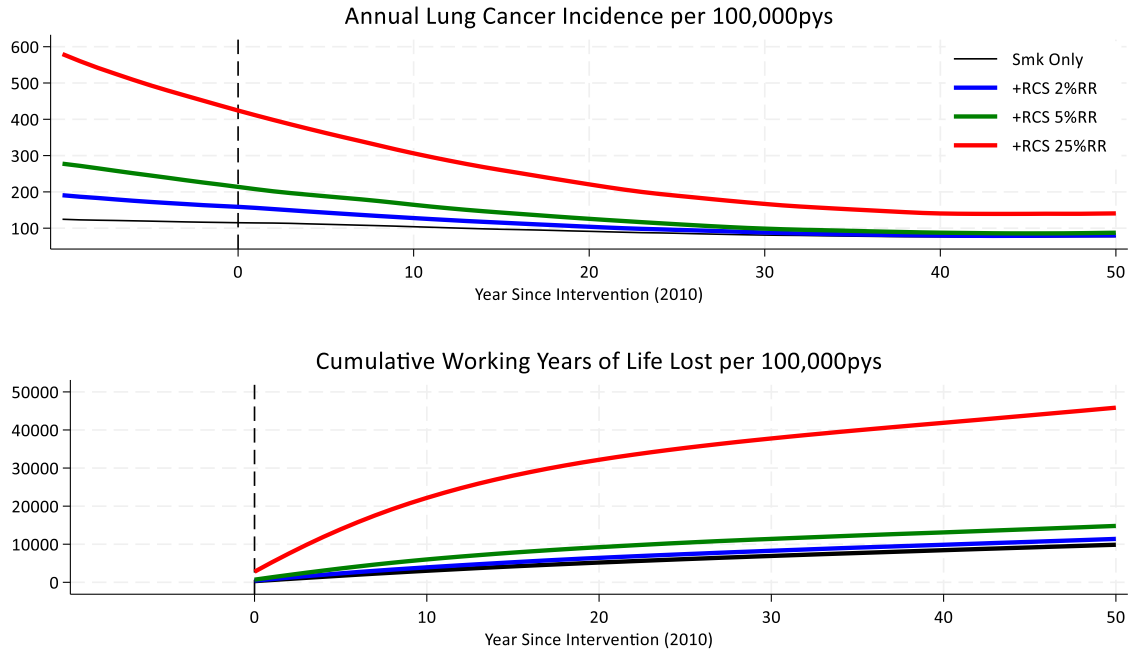
Table 7 - Summary statistics for five-year average around 10 year follow up years post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with Smoking Only Model

	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (smoking only)	114.9	104.5	91.3	80.3	76.4	77.5
...95%LCI Inc per 100000pys (smoking only)	114.5	104.1	91.0	80.1	76.1	77.2
...95%UCI Inc per 100000pys (smoking only)	115.2	104.8	91.6	80.6	76.7	77.8-
	.	.	.	.	.	.
Mean age (smoking only)	65.7	66.1	66.8	66.9	67.1	67.2
...95%LCI Inc per 100000pys (smoking only)	61.7	61.8	62.0	61.4	61.2	61.0
...95%UCI Inc per 100000pys (smoking only)	69.6	70.3	71.7	72.4	73.1	73.4
	.	.	.	.	.	.
Median age (smoking only)	65.7	66.1	67.0	67.1	67.5	67.5
...25th Percentile (smoking only)	60.0	60.6	61.1	61.3	61.3	61.3
...75th Percentile (smoking only)	71.5	71.9	72.8	73.1	73.4	73.6
	.	.	.	.	.	.
Working Years of life lost (smoking only)	296.4	246.4	186.2	159.2	147.7	146.1

Base Smoking Only Model + Working Life Exposure RCS

Table 8 summarise the annual incidence rates, WYLL, and patient characteristics at diagnosis, when RCS was included as an exposure i.e. the introduction of a single working life exposure. The results are repeated under three sizes of exposure-outcome risk set at 2% (blue), 5% (green), and 25% (red) increase in risk per unit increase in cumulative RCS exposure. Note, this model currently assumes that once exposure risk is experienced by the participant the risk of LC stays increased for the rest of their life.

Figure 6 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) comparing RCS percentage relative risk of 2% (blue), 5% (green), and 25% (red) increase per cumulative unit; Model only includes smoking and assumes no half-life decay in risk function.



The five year average annual incidence rates around the intervention year (2010) is then 159.3, 214.4, and 425.3 for 2%, 5%, and 25% respectively. Compared to 114.3 per 100,000 pys in the smoking only model, this equates to a 40%, 87%, and 373% increase in the annual risk, which drops after 40 years to be a 4%, 14%, and 82% increase compared to smoking only (76.4 per 100,000 pys). Similarly, age of LC diagnosis becomes earlier (60.1 for 25% risk vs 65.9 for 2% in 2010), and consequently WYLL increases (from 431 to 2762 in 2010).

Table 8 – Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with Smoking + RCS model, where RCS percentage Relative Risk is increasing from 2%, 5%, and 25%.

	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 2%RR)	159.3	127.8	104.1	87.7	79.6	79.8
...95%LCI Inc per 100000pys (+RCS 2%RR)	158.9	127.4	103.7	87.4	79.4	79.6
...95%UCI Inc per 100000pys (+RCS 2%RR)	159.7	128.2	104.4	88.0	79.9	80.1
Mean age (+RCS 2%RR)	65.9	66.8	67.3	67.4	67.4	67.3
...95%LCI Inc per 100000pys (+RCS 2%RR)	62.8	63.1	62.7	62.1	61.6	61.3
...95%UCI Inc per 100000pys (+RCS 2%RR)	69.1	70.6	71.8	72.7	73.2	73.2
Median age (+RCS 2%RR)	65.9	66.8	67.3	67.7	67.7	67.5
...25th Percentile (+RCS 2%RR)	60.3	61.2	61.5	61.4	61.5	61.3
...75th Percentile (+RCS 2%RR)	71.8	72.7	73.4	73.9	73.7	73.7
Working Years of life lost (+RCS 2%RR)	431.4	289.6	216.5	174.4	151.5	153.1

	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 5%RR)	214.4	164.3	125.8	98.2	87.3	87.5
...95%LCI Inc per 100000pys (+RCS 5%RR)	213.8	163.9	125.4	97.9	87.0	87.2
...95%UCI Inc per 100000pys (+RCS 5%RR)	214.9	164.8	126.2	98.5	87.6	87.8
Mean age (+RCS 5%RR)	65.3	66.7	67.7	67.9	67.9	67.7
...95%LCI Inc per 100000pys (+RCS 5%RR)	62.7	63.5	63.7	63.5	62.7	62.2
...95%UCI Inc per 100000pys (+RCS 5%RR)	67.9	69.8	71.6	72.4	73.1	73.1
Median age (+RCS 5%RR)	65.1	66.5	67.7	68.1	68.1	67.8
...25th Percentile (+RCS 5%RR)	59.3	60.9	61.7	62.1	62.0	61.8
...75th Percentile (+RCS 5%RR)	71.2	72.7	73.7	74.1	74.2	74.2
Working Years of life lost (+RCS 5%RR)	701.9	417.0	259.7	183.7	159.4	170.2

	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR)	425.3	305.4	220.8	166.7	139.7	143.4
...95%LCI Inc per 100000pys (+RCS 25%RR)	424.4	304.7	220.2	166.2	139.3	142.9
...95%UCI Inc per 100000pys (+RCS 25%RR)	426.1	306.1	221.3	167.2	140.2	143.8
Mean age (+RCS 25%RR)	61.0	63.5	65.6	66.7	66.8	66.5
...95%LCI Inc per 100000pys (+RCS 25%RR)	58.9	60.9	62.6	63.5	62.9	62.2
...95%UCI Inc per 100000pys (+RCS 25%RR)	63.1	66.1	68.5	69.8	70.6	70.8
Median age (+RCS 25%RR)	60.9	63.4	65.5	66.7	66.9	66.8
...25th Percentile (+RCS 25%RR)	54.3	57.1	59.5	60.5	60.5	60.1
...75th Percentile (+RCS 25%RR)	67.7	69.9	71.9	73.3	73.7	73.4
Working Years of life lost (+RCS 25%RR)	2767.6	1422.6	731.5	462.1	387.4	412.2

Base Smoking only Model + RCS (with Decaying Risk)

Assuming any increased risk remains for the rest of the individual's life may not be realistic. Figure 7 & Table 9 describe the results associated with decaying risk, were an individual increase in risk experienced is then assumed to dissipate over time. The speed of the dissipating risk defined in terms of a half-life decay, where every set number of years the risk due to exposure decreases by half. In this case we set that to 15 and 5 years, i.e. every 15 years the risk decreased by half. Note, we also include no half-life decay meaning any increase in risk is permanent. Figure 7 describes the annual incidence rates and cumulative WYLL for the three exposure-outcome risk relationships (2% (blue), 5% (green), and 25% (red) under three decaying risk scenarios none (solid), 15 year (long dash), and 5 year half-life decay. As half-life decay rate increases, annual incidence rates and working years of life lost tend towards the baseline model as the effect of exposure becomes less impactful. This is particularly strong effect with respect to large exposure-outcome risk relationship (25%) and faster half-life decay (5 year) , see dash red line, which becomes comparable to the a mild risk relationship (5%) but permanent increase in risk (no decay), see solid blue. The average age of diagnosis also increases as half-life decay increases, with the individuals not diagnosed until 2-3 years later in life.

Figure 7 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) comparing none (solid), 15 year (long dash), and 5 year (short dash) half-life decay for RCS percentage relative risk of 2% (blue), 5% (green), and 25% (red) increase per cumulative unit; Model only includes smoking (black)

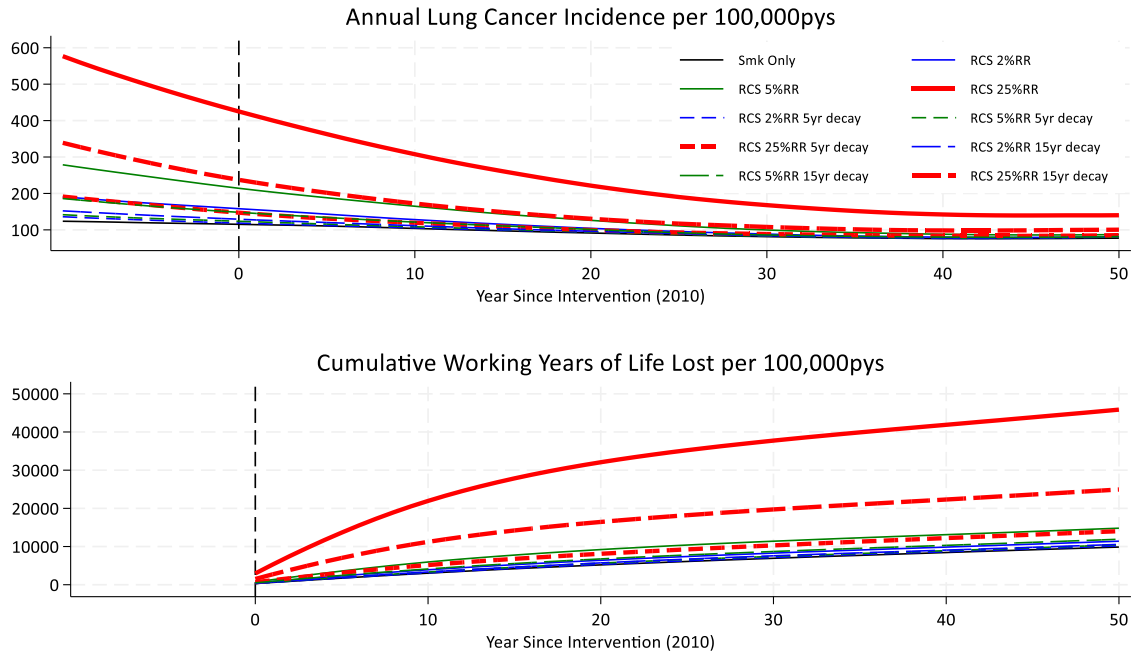


Table 9 – Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with with increasing half-life decay in RCS exposure risk (none, 15, and 5 year) for the Smoking + RCS model, where RCS percentage Relative Risk is 25% per unit increase

No Exposure Risk Decay	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR)	425.3	305.4	220.8	166.7	139.7	143.4
...95%LCI Inc per 100000pys (+RCS 25%RR)	424.4	304.7	220.2	166.2	139.3	142.9
...95%UCI Inc per 100000pys (+RCS 25%RR)	426.1	306.1	221.3	167.2	140.2	143.8
Mean age (+RCS 25%RR)	61.0	63.5	65.6	66.7	66.8	66.5
...95%LCI Inc per 100000pys (+RCS 25%RR)	58.9	60.9	62.6	63.5	62.9	62.2
...95%UCI Inc per 100000pys (+RCS 25%RR)	63.1	66.1	68.5	69.8	70.6	70.8
Median age (+RCS 25%RR)	60.9	63.4	65.5	66.7	66.9	66.8
...25th Percentile (+RCS 25%RR)	54.3	57.1	59.5	60.5	60.5	60.1
...75th Percentile (+RCS 25%RR)	67.7	69.9	71.9	73.3	73.7	73.4
Working Years of life lost (+RCS 25%RR)	2767.6	1422.6	731.5	462.1	387.4	412.2
Exposure Risk Decay – 15 year half-life	**Year since Intervention (2010)**					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR)	235.9	170.4	129.5	108.0	97.3	100.9
...95%LCI Inc per 100000pys (+RCS 25%RR)	235.3	169.9	129.2	107.6	97.0	100.6
...95%UCI Inc per 100000pys (+RCS 25%RR)	236.5	170.9	129.9	108.3	97.7	101.3
Mean age (+RCS 25%RR)	61.0	63.3	65.1	65.9	66.0	66.0
...95%LCI Inc per 100000pys (+RCS 25%RR)	58.1	60.1	61.3	61.3	60.8	60.5
...95%UCI Inc per 100000pys (+RCS 25%RR)	63.9	66.6	68.8	70.4	71.2	71.5
Median age (+RCS 25%RR)	61.3	63.4	65.3	66.2	66.5	66.4
...25th Percentile (+RCS 25%RR)	54.7	57.4	59.4	60.1	59.9	60.0
...75th Percentile (+RCS 25%RR)	67.7	69.5	71.2	72.3	72.6	72.5
Working Years of life lost (+RCS 25%RR)	1418.9	712.9	393.4	286.1	257.2	265.2
Exposure Risk Decay – 5 year half-life	**Year since Intervention (2010)**					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR)	146.4	120.1	98.9	88.3	83.3	85.3
...95%LCI Inc per 100000pys (+RCS 25%RR)	146.0	119.7	98.5	88.0	83.0	84.9
...95%UCI Inc per 100000pys (+RCS 25%RR)	146.8	120.5	99.2	88.6	83.6	85.6
Mean age (+RCS 25%RR)	63.0	64.7	65.8	66.3	66.7	66.7
...95%LCI Inc per 100000pys (+RCS 25%RR)	59.4	60.7	61.1	61.1	60.8	60.7
...95%UCI Inc per 100000pys (+RCS 25%RR)	66.7	68.8	70.6	71.6	72.5	72.7
Median age (+RCS 25%RR)	63.6	65.1	66.2	66.9	66.9	67.1
...25th Percentile (+RCS 25%RR)	57.3	59.1	60.2	60.4	60.8	60.9
...75th Percentile (+RCS 25%RR)	69.4	70.8	72.0	72.6	73.3	73.3
Working Years of life lost (+RCS 25%RR)	616.1	374.2	241.7	204.0	180.4	185.6

Base Smoking only Model + RCS (decaying risk) + Diesel Fumes

Figure 8 & Table 10 repeat the model in Section 0 but now includes the additional co-exposure Diesel fumes, effectively expanding the model to include a manipulable multi-exposure exposome. This model assumes that each exposure is independent of each other, i.e. someone exposed to a high level of smoking is not also exposed to a high level of RCS, or Diesel Fumes. Figure 8 & Table 10 report the results assuming the RCS exposure-outcome relationship is 25% per unit increase in cumulative exposure of RCS. This is to highlight any differences that have occurred. This model assumes that each exposure is independent of each other, i.e. someone exposed to a high level of smoking is not also exposed to a high level of RCS, or Diesel Fumes. The inclusion of Diesel Fumes has simply acted as an additive effect, similar to RCS when added to the Smoking only Model. This has resulted in an increase in incidence rate, and WYLL, though little change has occurred in the year of diagnosis.

Figure 8 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) comparing none (solid), 15 year (long dash), and 5 year (short dash) half-life decay for RCS (red) and RCS + Diesel Fumes (green) models; Model includes smoking & RCS percentage Relative Risk increase is 25%

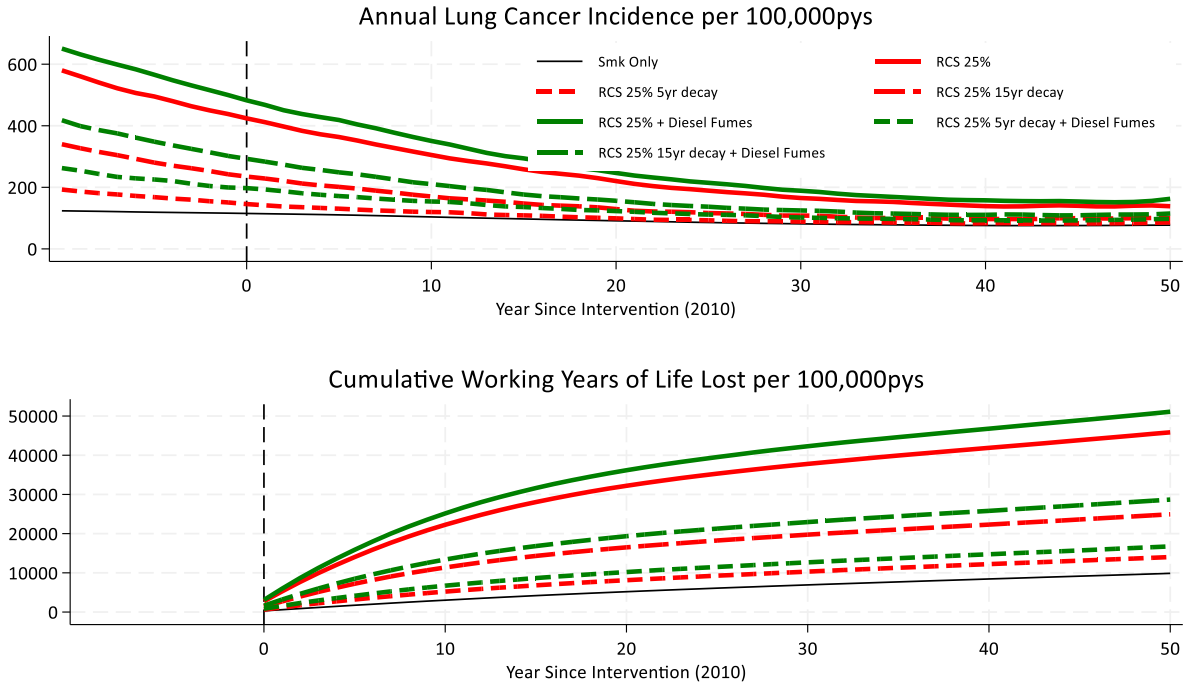


Table 10 - Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with and without additional co-exposure Diesel Fumes in the Smoking + RCS model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (none, 15, and 5 year)

15-year half-life RCS decay + No Diesel Fumes	Year since Intervention (2010)					
	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR)	235.9	170.4	129.5	108.0	97.3	100.9
...95%LCI Inc per 100000pys (+RCS 25%RR)	235.3	169.9	129.2	107.6	97.0	100.6
...95%UCI Inc per 100000pys (+RCS 25%RR)	236.5	170.9	129.9	108.3	97.7	101.3
Mean age (+RCS 25%RR)	61.0	63.3	65.1	65.9	66.0	66.0
...95%LCI Inc per 100000pys (+RCS 25%RR)	58.1	60.1	61.3	61.3	60.8	60.5
...95%UCI Inc per 100000pys (+RCS 25%RR)	63.9	66.6	68.8	70.4	71.2	71.5
Median age (+RCS 25%RR)	61.3	63.4	65.3	66.2	66.5	66.4
...25th Percentile (+RCS 25%RR)	54.7	57.4	59.4	60.1	59.9	60.0
...75th Percentile (+RCS 25%RR)	67.7	69.5	71.2	72.3	72.6	72.5
Working Years of life lost (+RCS 25%RR)	1418.9	712.9	393.4	286.1	257.2	265.2
15-year half-life RCS decay + Diesel Fumes	**0**	**10**	**20**	**30**	**40**	**50**
Inc per 100000pys (+RCS 25%RR+DF)	292.9	210.1	155.9	125.0	111.3	114.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	292.2	209.6	155.5	124.6	111.0	113.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	293.6	210.6	156.4	125.4	111.7	114.4
Mean age (+RCS 25%RR+DF)	61.6	63.9	65.7	66.4	66.5	66.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	59.0	60.8	62.4	62.3	62.1	61.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	64.2	66.9	69.0	70.4	70.9	71.2
Median age (+RCS 25%RR+DF)	61.8	64.0	65.8	66.7	66.9	66.7
...25th Percentile (+RCS 25%RR+DF)	55.4	58.1	59.9	60.6	60.6	60.6
...75th Percentile (+RCS 25%RR+DF)	68.2	69.9	71.8	72.8	73.0	72.7
Working Years of life lost (+RCS 25%RR+DF)	1680.9	847.7	460.8	318.9	276.6	297.2
5-year half-life RCS decay + No Diesel Fumes	**0**	**10**	**20**	**30**	**40**	**50**
Inc per 100000pys (+RCS 25%RR)	146.4	120.1	98.9	88.3	83.3	85.3
...95%LCI Inc per 100000pys (+RCS 25%RR)	146.0	119.7	98.5	88.0	83.0	84.9
...95%UCI Inc per 100000pys (+RCS 25%RR)	146.8	120.5	99.2	88.6	83.6	85.6
Mean age (+RCS 25%RR)	63.0	64.7	65.8	66.3	66.7	66.7
...95%LCI Inc per 100000pys (+RCS 25%RR)	59.4	60.7	61.1	61.1	60.8	60.7
...95%UCI Inc per 100000pys (+RCS 25%RR)	66.7	68.8	70.6	71.6	72.5	72.7
Median age (+RCS 25%RR)	63.6	65.1	66.2	66.9	66.9	67.1
...25th Percentile (+RCS 25%RR)	57.3	59.1	60.2	60.4	60.8	60.9
...75th Percentile (+RCS 25%RR)	69.4	70.8	72.0	72.6	73.3	73.3
Working Years of life lost (+RCS 25%RR)	616.1	374.2	241.7	204.0	180.4	185.6
5-year half-life RCS decay + Diesel Fumes	**0**	**10**	**20**	**30**	**40**	**50**
Inc per 100000pys (+RCS 25%RR+DF)	195.8	154.4	122.5	102.6	92.7	97.5
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	195.3	154.0	122.1	102.2	92.4	97.2
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	196.3	154.9	122.9	102.9	93.0	97.9
Mean age (+RCS 25%RR+DF)	63.8	65.5	66.6	66.8	67.2	67.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	60.8	62.2	62.7	62.3	62.0	61.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF	66.8	68.8	70.5	71.4	72.4	72.5
Median age (+RCS 25%RR+DF)	64.0	65.6	66.8	67.1	67.5	67.2
...25th Percentile (+RCS 25%RR+DF)	58.1	60.0	60.9	61.0	61.4	61.1
...75th Percentile (+RCS 25%RR+DF)	70.0	71.4	72.6	73.0	73.6	73.4
Working Years of life lost (+RCS 25%RR+DF)	800.2	456.1	291.7	228.6	196.4	215.3

Modifying the Correlations Between Exposures?

As noted, the model currently assumes each exposure occurs independently of each other, i.e. someone exposed to a high level of smoking is not also more likely to be exposed to a high level of RCS, or Diesel Fumes. In reality this is unlikely to have happened, particularly with respect to workplace exposures such as RCS and Diesel Fumes but also lifestyle factors, such as smoking, can often correlate due to behaviour. Here we provide the results for a scenario where between

exposure correlation has been increased to 0.5 for all three exposures (i.e. what is considered a large correlation even for workplace exposures). We also used a bespoke correlation, where workplace exposures were highly correlated (0.5) but lifestyle factors were only moderately correlated (0.1). This is not reported here, as we only wish to understand the influence of correlation. We use the bespoke model, later to explore the intervention effects. Figure 9 and Table 11 summarise the results for the Smoking, RCS, and Diesel model where between exposure correlations were independent (=0, green) and strong (0.5, blue). The results represent RCS cumulative exposure-outcome relative risk at 25% per unit increase, and the three decaying risk functions (none, 15, 5 year half-life). Results appear to indicate that there is a small increase in the incidence rate of LC when exposures are independent, this occurs more prominently prior to the intervention year 2010 (see

Figure 10 for full study period 1960 to 2060), when rates peak due to more extreme exposures. This may be due to pooling of higher exposures in fewer people, as of you are already a heavy smoker with strong likelihood of having LC, adding high levels of RCS exposure will have little effect on the overall incidence. Where as mild or moderate smokers who were at moderate risk, to then add moderate of severe RCS exposure, means more of the population at risk of developing LC. The post 2010 intervention period, does not appear to have this effect occurring. Possible due to the lower levels of exposure experienced by participants making it harder for the pooling affect to play a part.

Figure 9 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) for between exposures correlation 0.5 (Blue) vs 0 (Green) i.e. independent; Smoking + RCS + Diesel Fumes Model, with 25% Relative Risk, and half-life decay function (none, 15 year, and 5 year)

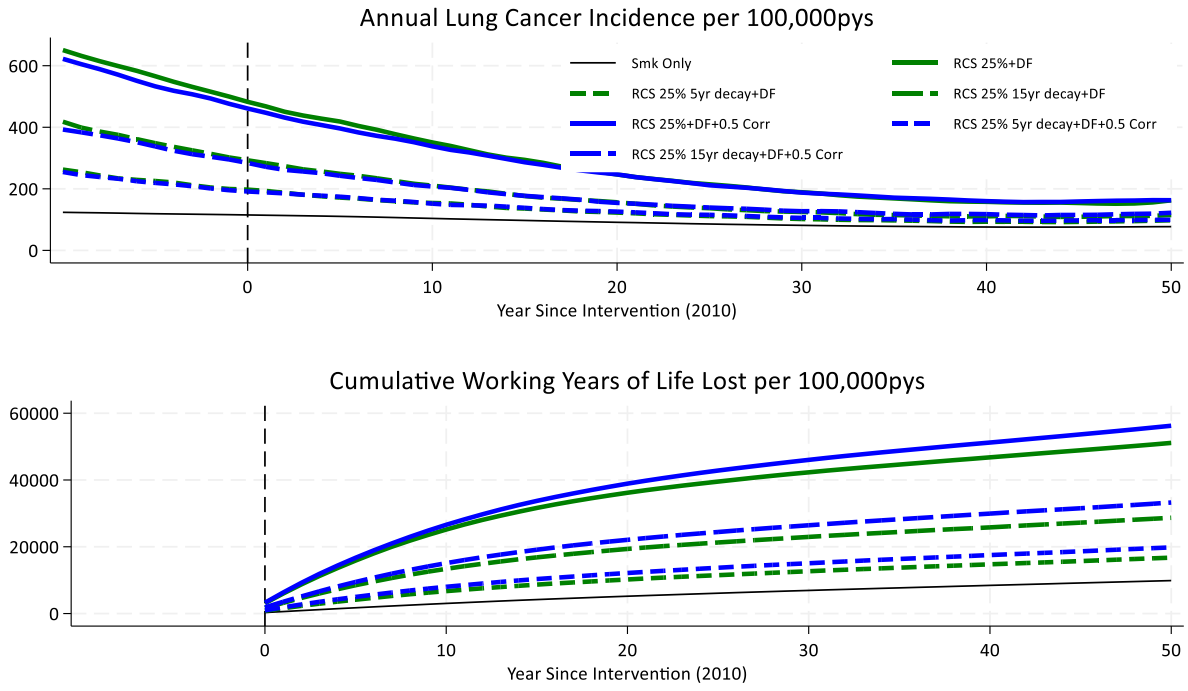


Figure 10 - Annual Incidence Rates for full study period (1960-2060) for between exposures correlation 0.5 (Blue) vs 0 (Green) i.e. independent; Smoking + RCS + Diesel Fumes Model, with 25% Relative Risk, and half-life decay function (none, 15 year, and 5 year)

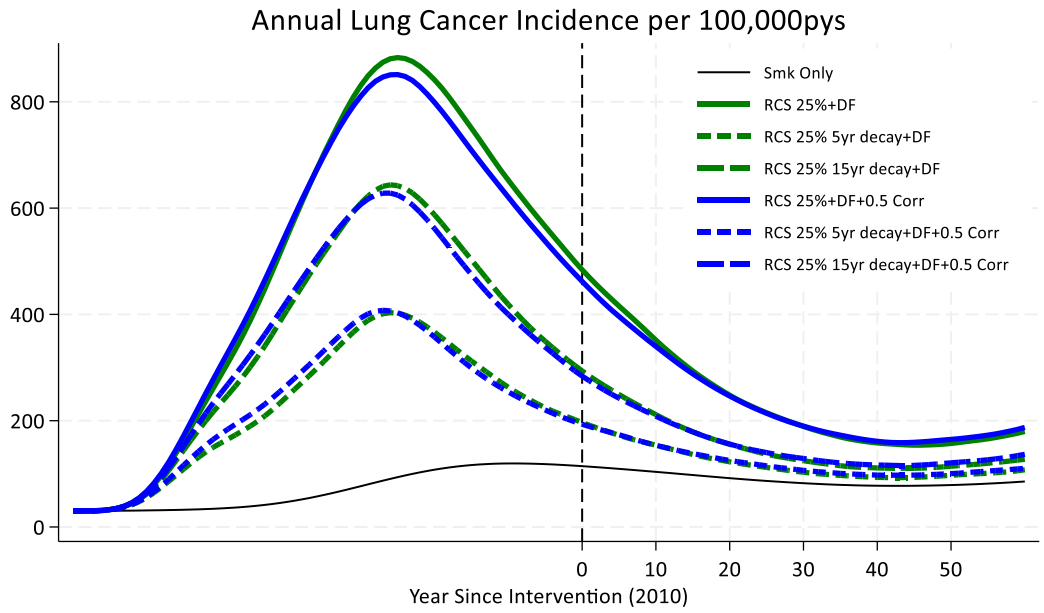


Table 11 – Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with between exposure correlation of 0 (i.e. independent) and 0.5 (i.e. strong correlation) in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year).

	Year since Intervention (2010)					
15-year half-life RCS decay + Diesel Fumes + 0 CORR	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF)	292.9	210.1	155.9	125.0	111.3	114.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	292.2	209.6	155.5	124.6	111.0	113.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	293.6	210.6	156.4	125.4	111.7	114.4
Mean age (+RCS 25%RR+DF)	61.6	63.9	65.7	66.4	66.5	66.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	59.0	60.8	62.4	62.3	62.1	61.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	64.2	66.9	69.0	70.4	70.9	71.2
Median age (+RCS 25%RR+DF)	61.8	64.0	65.8	66.7	66.9	66.7
...25th Percentile (+RCS 25%RR+DF)	55.4	58.1	59.9	60.6	60.6	60.6
...75th Percentile (+RCS 25%RR+DF)	68.2	69.9	71.8	72.8	73.0	72.7
Working Years of life lost (+RCS 25%RR+DF)	1680.9	847.7	460.8	318.9	276.6	297.2
15-year half-life RCS decay + Diesel Fumes + 0.5 CORR	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	283.1	208.0	155.4	128.8	117.1	121.2
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	282.4	207.4	154.9	128.4	116.7	120.8
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	283.8	208.5	155.8	129.2	117.4	121.6
Mean age (+RCS 25%RR+DF+0.5Corr)	60.6	62.9	64.8	65.5	65.6	65.6
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	58.0	60.0	61.4	61.3	61.4	61.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	63.1	65.7	68.2	69.6	69.8	70.2
Median age (+RCS 25%RR+DF+0.5Corr)	60.7	62.9	65.0	65.7	65.9	65.9
...25th Percentile (+RCS 25%RR+DF+0.5Corr)	53.9	56.6	58.7	59.6	59.6	59.5
...75th Percentile (+RCS 25%RR+DF+0.5Corr)	67.4	69.1	71.1	71.8	72.1	72.1
Working Years of life lost (+RCS 25%RR+DF+0.5Corr)	1845.5	980.7	532.9	382.1	337.7	360.7
5-year half-life RCS decay + Diesel Fumes + 0 CORR	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF)	195.8	154.4	122.5	102.6	92.7	97.5
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	195.3	154.0	122.1	102.2	92.4	97.2
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	196.3	154.9	122.9	102.9	93.0	97.9
Mean age (+RCS 25%RR+DF)	63.8	65.5	66.6	66.8	67.2	67.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF)	60.8	62.2	62.7	62.3	62.0	61.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF)	66.8	68.8	70.5	71.4	72.4	72.5
Median age (+RCS 25%RR+DF)	64.0	65.6	66.8	67.1	67.5	67.2
...25th Percentile (+RCS 25%RR+DF)	58.1	60.0	60.9	61.0	61.4	61.1
...75th Percentile (+RCS 25%RR+DF)	70.0	71.4	72.6	73.0	73.6	73.4
Working Years of life lost (+RCS 25%RR+DF)	800.2	456.1	291.7	228.6	196.4	215.3
15-year half-life RCS decay + Diesel Fumes + 0.5 CORR	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	192.4	153.0	125.7	106.6	97.5	100.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	191.9	152.5	125.3	106.2	97.2	99.7
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	192.9	153.5	126.1	106.9	97.9	100.4
Mean age (+RCS 25%RR+DF+0.5Corr)	62.5	64.4	65.8	66.3	66.5	66.6
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	59.3	60.7	61.8	61.7	61.8	61.4
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+0.5Corr)	65.7	68.2	69.8	71.0	71.2	71.8
Median age (+RCS 25%RR+DF+0.5Corr)	62.8	64.5	65.9	66.4	66.8	66.8
...25th Percentile (+RCS 25%RR+DF+0.5Corr)	56.3	58.5	60.0	60.4	60.6	60.7
...75th Percentile (+RCS 25%RR+DF+0.5Corr)	69.2	70.5	71.8	72.7	72.8	72.9
Working Years of life lost (+RCS 25%RR+DF+0.5Corr)	951.2	542.8	341.8	260.9	229.4	237.1

Results - Exposure Intervention Effects

This section describes the results of stage two of the study, where we apply three interventions associated with a reduction in the average exposure experienced by all workers (initially set at 30%), and a limit on the maximum exposure experienced (maximum set to 75th Percentile). These are defined by the exposure experienced in 2010, and assumed to start in 2010. These interventions are initially applied only to RCS (the main workplace exposure) but then subsequently applied to both RCS and Diesel Fumes (effectively an unintended consequence).

Reduction in Average Exposure (30%) - Applied to RCS Only

Figure 11 & Table 12 report the results associated with 30% reduction in the average exposure (yellow) vs not (blue) in the full model with 25% increased risk of LC per unit increase in cumulative RCS, decay risk function at none, 15 year, and 5 year half-life, and the bespoke between-exposure correlation. Though small improvements are observed in the incidence rates after 10 years for both 15-year and 5-year half-life decay (incidence rate reduced by ~2 per 100,000pys in both cases), improvements don't begin to occur until 20 plus years post intervention. This is likely to be due to the latency period meaning any intervention effect will be delayed. Incidence rates 20 years later are reduced by 6 per 100,000pys and 4 per 100,000pys for 15 year and 5 years respectively, 30 years later its 8 per 100,000pys and 4 per 100,000pys, 40 years later its 12 per 100,000pys and 2 per 100,000pys.

Figure 11 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) with (yellow) and without (blue) 30% reduction in average exposure; Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & bespoke between exposure correlation

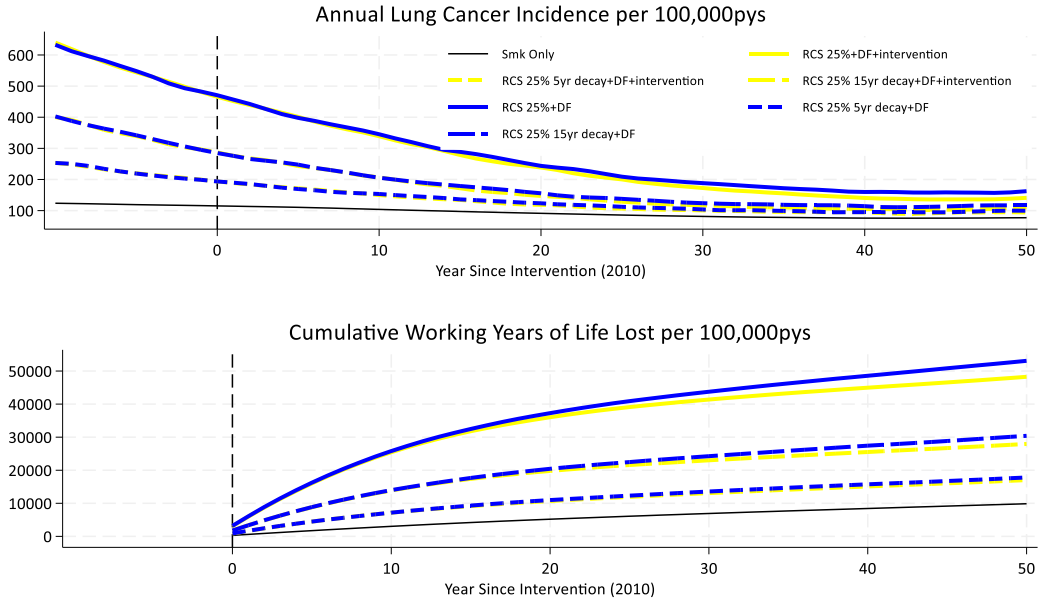


Table 12 - Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with and without 30% reduction in average exposure intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke.

	Year since Intervention (2010)					
15-year half-life RCS decay + Diesel Fumes	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.7	207.0	154.6	124.1	113.9	118.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.1	206.5	154.1	123.7	113.5	118.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	286.4	207.6	155.0	124.5	114.2	118.8
Mean age (+RCS 25%RR+DF+besCorr)	61.0	63.4	65.1	66.1	66.4	66.2
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	58.5	60.4	61.8	62.4	62.2	61.8
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	63.5	66.4	68.4	69.9	70.5	70.7
Median age (+RCS 25%RR+DF+besCorr)	61.2	63.4	65.3	66.5	66.8	66.4
...25th Percentile (+RCS 25%RR+DF+besCorr)	54.7	57.4	59.3	60.3	60.5	60.1
...75th Percentile (+RCS 25%RR+DF+besCorr)	67.6	69.6	71.1	72.4	72.9	72.6
Working Years of life lost (+RCS 25%RR+DF+besCorr)	1765.5	892.9	486.7	330.6	292.7	318.0

	Year since Intervention (2010)					
15-year half-life RCS decay + Diesel intervention	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.9	205.7	148.0	116.9	105.5	109.3
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.3	205.2	147.6	116.6	105.2	109.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	286.5	206.2	148.5	117.3	105.9	109.7
Mean age (+RCS 25%RR+DF+besCorr)	61.1	63.5	65.6	66.7	66.7	66.8
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	58.5	60.6	62.3	62.9	62.0	62.1
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	63.8	66.5	68.9	70.4	71.4	71.5
Median age (+RCS 25%RR+DF+besCorr)	61.2	63.5	65.7	66.7	66.9	67.2
...25th Percentile (+RCS 25%RR+DF+besCorr)	54.7	57.5	60.0	61.0	60.9	60.9
...75th Percentile (+RCS 25%RR+DF+besCorr)	67.7	69.7	71.6	72.7	73.1	73.2
Working Years of life lost (+RCS 25%RR+DF+besCorr)	1746.2	875.1	422.7	273.1	248.7	261.3

	Year since Intervention (2010)					
5-year half-life RCS decay + Diesel Fumes	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.5	152.4	122.8	103.9	95.0	99.7
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.0	151.9	122.4	103.5	94.7	99.3
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.0	152.8	123.2	104.2	95.3	100.0
Mean age (+RCS 25%RR+DF+besCorr)	63.1	65.0	66.4	66.7	67.0	66.9
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	59.9	61.4	62.4	62.3	62.1	61.8
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	66.3	68.6	70.4	71.0	72.0	72.0
Median age (+RCS 25%RR+DF+besCorr)	63.4	65.1	66.4	66.8	67.2	67.2
...25th Percentile (+RCS 25%RR+DF+besCorr)	57.2	59.2	60.7	60.8	61.0	61.0
...75th Percentile (+RCS 25%RR+DF+besCorr)	69.4	71.0	72.3	73.0	73.5	73.2
Working Years of life lost (+RCS 25%RR+DF+besCorr)	874.4	495.1	296.9	242.0	202.1	224.1

	Year since Intervention (2010)					
5-year half-life RCS decay + Diesel Intervention	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.2	150.4	118.4	100.7	93.7	95.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	193.7	149.9	118.1	100.4	93.3	94.7
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.7	150.8	118.8	101.0	94.0	95.4
Mean age (+RCS 25%RR+DF+besCorr)	63.1	65.0	66.6	67.0	67.2	67.2
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	60.0	61.4	62.3	62.5	62.2	62.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	66.1	68.7	70.8	71.5	72.1	72.4
Median age (+RCS 25%RR+DF+besCorr)	63.4	65.1	66.7	67.1	67.5	67.4
...25th Percentile (+RCS 25%RR+DF+besCorr)	57.2	59.3	60.9	61.3	61.3	61.3
...75th Percentile (+RCS 25%RR+DF+besCorr)	69.4	71.0	72.5	73.2	73.6	73.7
Working Years of life lost (+RCS 25%RR+DF+besCorr)	873.4	477.2	281.8	214.2	195.0	202.5

Max limit of Exposure (75th Percentile) – Applied RCS Only

Figure 12 & Table 13 similarly report the results associated with setting the max level exposure to be the intervention years 75th percentile (yellow) vs not (blue). This applied to the full model containing all three exposures with a 25% increased risk of LC per unit increase in cumulative RCS, decay risk function set to be none, 15 year, and 5 year half-life, and the bespoke between-exposure correlation. Intervention effects on annual incidence rates appear to occur faster than average reduction, with 10 year follow-up point difference in incidence rates at 5.6 per 100,000pys and 2 per 100,000pys for 15 and 5 years decay respectively. This increased to 14.6 per 100,000pys and 16.8 per 100,000pys at 20 and 30 years later for 15-year decay, whereas for 5-year decay it increased to 5.8 per 100,000pys and 6.8 per 100,000pys at 20 and 30 years follow up. The average age of diagnosis appears to increase by approximated 1 year for both interventions compared to no intervention.

Figure 12 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) with (yellow) and without (blue) Max limit set to 75th Percentile; Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & between exposure correlation of 0.5 vs 0 (independent)

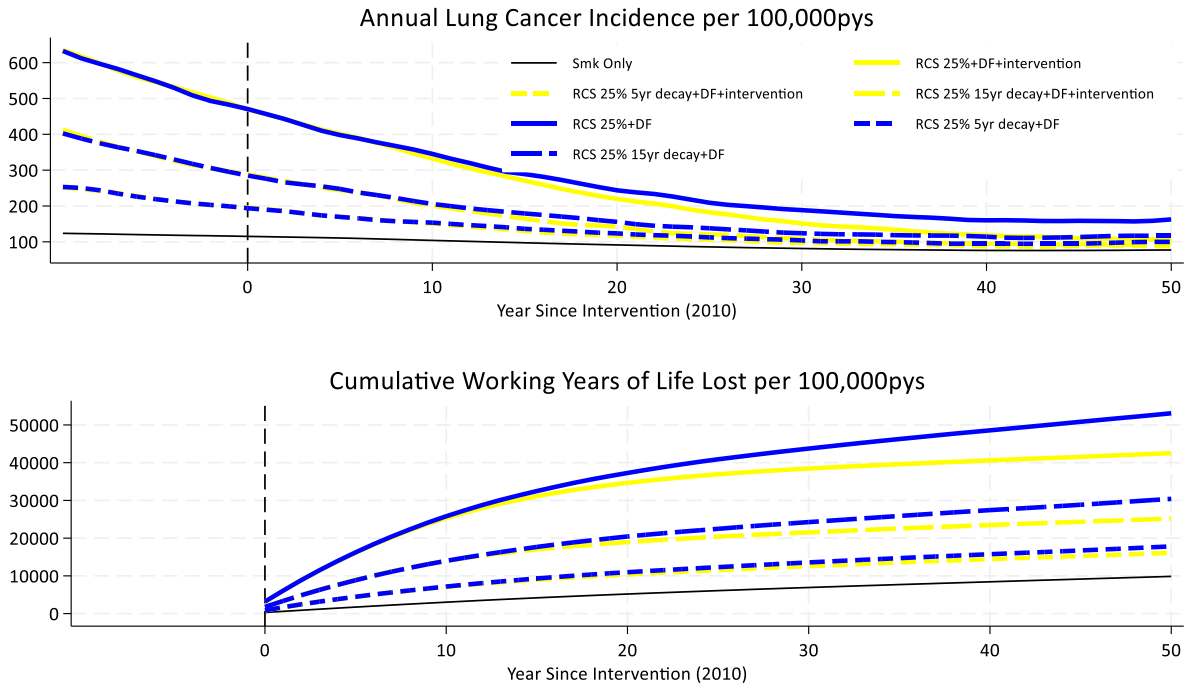


Table 13 - Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with and without Max Limit of exposure at 75th percentile intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke.

	Year since Intervention (2010)					
15-year half-life RCS decay + Diesel Fumes	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.7	207.0	154.6	124.1	113.9	118.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.1	206.5	154.1	123.7	113.5	118.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	286.4	207.6	155.0	124.5	114.2	118.8
Mean age (+RCS 25%RR+DF+besCorr)	61.0	63.4	65.1	66.1	66.4	66.2
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	58.5	60.4	61.8	62.4	62.2	61.8
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	63.5	66.4	68.4	69.9	70.5	70.7
Median age (+RCS 25%RR+DF+besCorr)	61.2	63.4	65.3	66.5	66.8	66.4
...25th Percentile (+RCS 25%RR+DF+besCorr)	54.7	57.4	59.3	60.3	60.5	60.1
...75th Percentile (+RCS 25%RR+DF+besCorr)	67.6	69.6	71.1	72.4	72.9	72.6
Working Years of life lost (+RCS 25%RR+DF+besCorr)	1765.5	892.9	486.7	330.6	292.7	318.0

	Year since Intervention (2010)					
15-year half-life RCS decay + Diesel Intervention	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	287.7	201.4	140.0	108.4	95.0	94.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	287.1	200.8	139.6	108.0	94.6	94.1
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	288.4	201.9	140.4	108.7	95.3	94.7
Intervention Relative Risk	1.0	1.0	0.9	0.9	0.8	0.8
Mean age (+RCS 25%RR+DF+besCorr)	61.1	63.7	66.3	67.4	67.6	67.6
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	58.5	60.7	62.9	63.3	62.4	62.5
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	63.7	66.7	69.7	71.5	72.9	72.7
Median age (+RCS 25%RR+DF+besCorr)	61.3	63.7	66.2	67.5	67.9	67.8
...25th Percentile (+RCS 25%RR+DF+besCorr)	54.7	57.6	60.8	61.9	62.0	61.7
...75th Percentile (+RCS 25%RR+DF+besCorr)	67.7	69.8	72.0	73.1	73.7	73.8
Working Years of life lost (+RCS 25%RR+DF+besCorr)	1758.2	831.2	342.5	212.4	181.3	185.3

	Year since Intervention (2010)					
5-year half-life RCS decay + Diesel Fumes	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.5	152.4	122.8	103.9	95.0	99.7
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.0	151.9	122.4	103.5	94.7	99.3
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.0	152.8	123.2	104.2	95.3	100.0
Mean age (+RCS 25%RR+DF+besCorr)	63.1	65.0	66.4	66.7	67.0	66.9
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	59.9	61.4	62.4	62.3	62.1	61.8
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	66.3	68.6	70.4	71.0	72.0	72.0
Median age (+RCS 25%RR+DF+besCorr)	63.4	65.1	66.4	66.8	67.2	67.2
...25th Percentile (+RCS 25%RR+DF+besCorr)	57.2	59.2	60.7	60.8	61.0	61.0
...75th Percentile (+RCS 25%RR+DF+besCorr)	69.4	71.0	72.3	73.0	73.5	73.2
Working Years of life lost (+RCS 25%RR+DF+besCorr)	874.4	495.1	296.9	242.0	202.1	224.1

	Year since Intervention (2010)					
5-year half-life RCS decay + Diesel Intervention	0	10	20	30	40	50
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.3	150.1	116.4	97.1	88.4	89.9
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.7	149.7	116.0	96.8	88.1	89.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.8	150.6	116.8	97.4	88.8	90.2
Intervention Relative Risk	1.0	1.0	0.9	0.9	0.9	0.9
Mean age (+RCS 25%RR+DF+besCorr)	63.1	65.2	66.7	67.3	67.4	67.5
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	60.2	61.7	62.8	62.6	62.2	62.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	66.1	68.6	70.6	72.0	72.7	73.1
Median age (+RCS 25%RR+DF+besCorr)	63.4	65.2	66.8	67.4	67.6	67.8
...25th Percentile (+RCS 25%RR+DF+besCorr)	57.2	59.5	61.2	61.6	61.5	61.8
...75th Percentile (+RCS 25%RR+DF+besCorr)	69.6	71.0	72.6	73.5	73.7	73.6
Working Years of life lost (+RCS 25%RR+DF+besCorr)	872.3	465.3	262.9	199.2	175.2	170.0

Comparing Intervention types (30% Ave vs 75th Max Limit)

Figure 13 & Table 14 compare the effect of the two intervention types, 30% reduction in exposure vs 75th percentile max exposure limit. Table 14 reports relative risks comparing the two intervention types against no intervention. The relative risk for the 5 year half-life decay for both interventions are smaller than the 15 year half-life in both interventions. This may be reflective of the shorter period of time that exposure can have an effect on risk of LC. In each case the maximum limit exposure intervention consistently indicated a larger relative risk effect, with improvements of 13% and 17% lower incidence 30 years after intervention. In almost all follow up points the 30% reduced exposure average appeared to have minimal effect when exposure decay function is fast 5-year half-life.

Figure 13 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) without (blue and with 30% reduction in average exposure (yellow) or Max limit set to 75th Percentile (orange); Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & between exposure correlation of 0.5 vs 0 (independent)

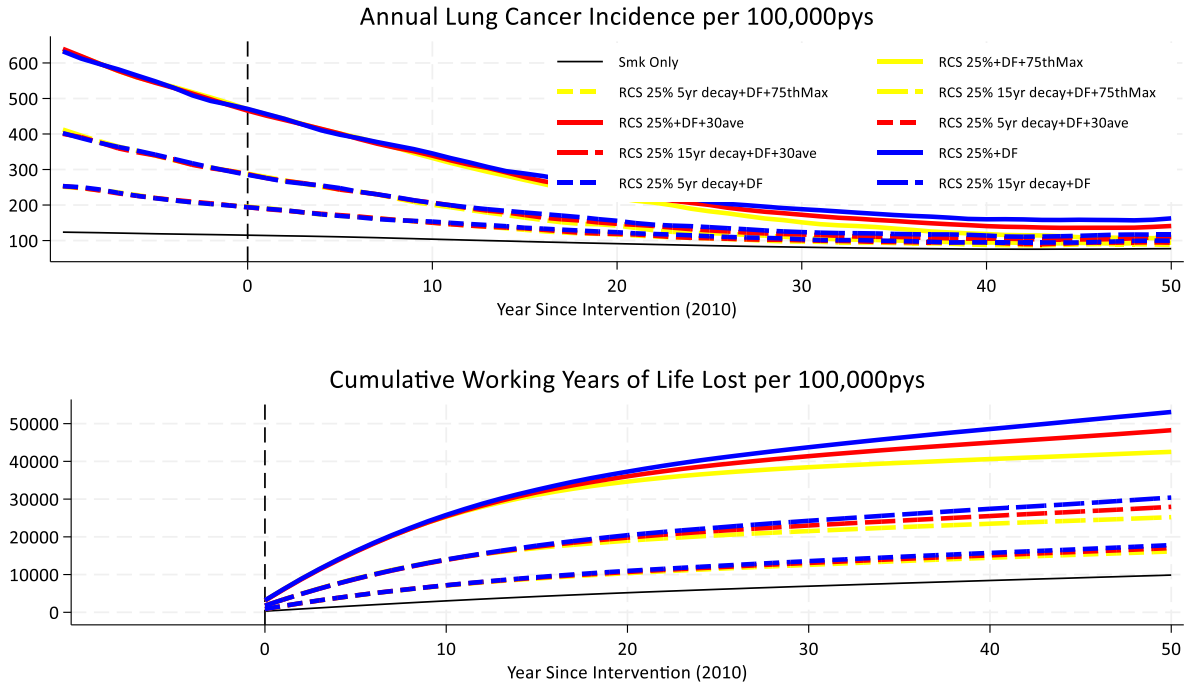


Table 14 - Summary statistics for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with 30% reduced average exposure reduced vs Max Limit of exposure at 75th percentile intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke, and intervention only applied to RCS.

	Year since Intervention (2010)					
15 year half-life decay	0	10	20	30	40	50
No Intervention						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.7	207.0	154.6	124.1	113.9	118.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.1	206.5	154.1	123.7	113.5	118.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	286.4	207.6	155.0	124.5	114.2	118.8
Intervention - 30% Ave Reduction						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.9	205.7	148.0	116.9	105.5	109.3
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	285.3	205.2	147.6	116.6	105.2	109.0
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	286.5	206.2	148.5	117.3	105.9	109.7
Intervention – 75th Percentile Max Limit						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	287.7	201.4	140.0	108.4	95.0	94.4
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	287.1	200.8	139.6	108.0	94.6	94.1
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	288.4	201.9	140.4	108.7	95.3	94.7

	Year since Intervention (2010)					
5 year half-life decay	0	10	20	30	40	50
No Intervention						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.5	152.4	122.8	103.9	95.0	99.7
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.0	151.9	122.4	103.5	94.7	99.3
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.0	152.8	123.2	104.2	95.3	100.0
Intervention - 30% Ave Reduction						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.2	150.4	118.4	100.7	93.7	95.0
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	193.7	149.9	118.1	100.4	93.3	94.7
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.7	150.8	118.8	101.0	94.0	95.4
Intervention – 75th Percentile Max Limit						
Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.3	150.1	116.4	97.1	88.4	89.9
...95%LCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	194.7	149.7	116.0	96.8	88.1	89.6
...95%UCI Inc per 100000pys (+RCS 25%RR+DF+besCorr)	195.8	150.6	116.8	97.4	88.8	90.2

	Year since Intervention (2010)					
Relative Risk Intervention v Not	0	10	20	30	40	50
Intervention Relative Risk - 30 Ave – 15yr decay	1.00	0.99	0.96	0.94	0.93	0.92
Intervention Relative Risk - 75th Max – 15yr decay	1.00	0.97	0.91	0.87	0.83	0.80
Intervention Relative Risk - 30 Ave – 5yr decay	1.00	0.99	0.96	0.97	0.99	0.95
Intervention Relative Risk - 75th Max – 5yr decay	1.00	0.99	0.95	0.94	0.93	0.90

Interventions Applied to Both RCS & Diesel Fumes, Compared to RCS Only

Table 15, allows for the comparison of the relative risk associated with the two intervention effects, where the interventions are applied first to the main exposure (RCS) and then repeated such that it was applied to both the main exposure and the co-exposure (Diesel Fumes). Though relative risks are consistently increased when interventions are applied to both exposures, the improvements are still only consistently seen after 10 years since the interventions are applied. Once again the faster half-life decay, results in a limited effect being observed even when the intervention is applied to the co-exposure as well.

Table 15 – Relative Risks for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with 30% reduced average exposure reduced vs Max Limit of exposure at 75th percentile intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke, and intervention applied to both RCS and RCS & Diesel.

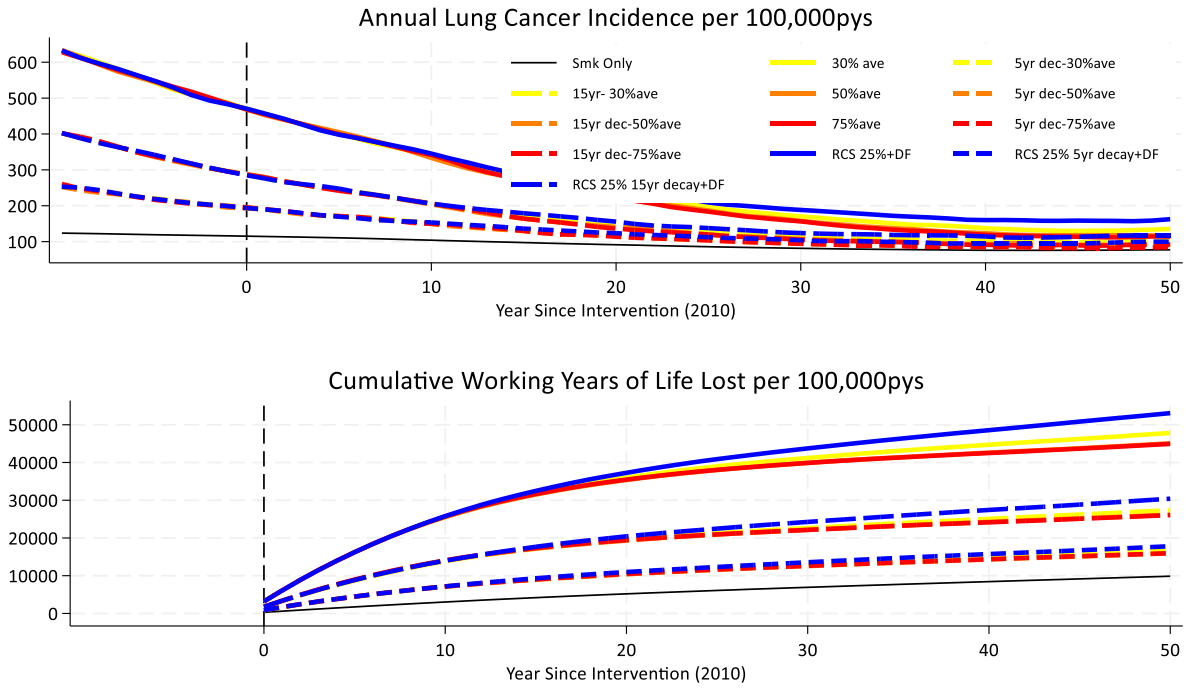
	Year since Intervention (2010)					
	0	10	20	30	40	50
Intervention Relative Risk - 30 Ave RCS only – 15yr Decay	1.00	0.99	0.96	0.94	0.93	0.92
Intervention Relative Risk - 75th Max RCS only – 15yr Decay	1.00	0.97	0.91	0.87	0.83	0.80
Intervention Relative Risk - 30 Ave RCS & DF – 15yr Decay	1.00	0.99	0.93	0.91	0.90	0.88
Intervention Relative Risk - 75th Max RCS & DF – 15yr Decay	1.00	0.97	0.88	0.83	0.78	0.75
Intervention Relative Risk - 30 Ave RCS only – 5yr Decay	1.00	0.99	0.96	0.97	0.99	0.95
Intervention Relative Risk - 75th Max RCS only – 5yr Decay	1.00	0.99	0.95	0.94	0.93	0.90
Intervention Relative Risk - 30 Ave RCS & DF – 5yr Decay	1.00	1.00	0.96	0.94	0.95	0.91
Intervention Relative Risk - 75th Max RCS & DF – 5yr Decay	1.00	0.99	0.92	0.91	0.88	0.87

Increasing the Size of Intervention

Additional exploratory work was performed that increased the size of the intervention effects such that reduction in the average exposure was increased to 50% and 75% (see Figure 14), and the max limit reduced to the 50th and 25th percentile (see Figure 15). Table 16 then reports the relative risks associated with each intervention effect for comparison, indicating the magnitude of the effect experienced due to each intervention. In each case here we have reported the effects observed when applied to both main and co-exposure. Interestingly there appears to be diminishing returns once the exposure intervention effect is reduced below 50% or the 50th percentile, i.e. the improvement in risk is marginal when extended to 25% or the 25th percentile.

Reducing the Average Exposure by 50% & 75%?

Figure 14 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) without (blue and with 30%, 50% & 75% reduction in average exposure (yellow, orange, red); Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & between exposure correlation of 0.5 vs 0 (independent)



Limiting the Maximum Exposure to the 50th& 25th percentile

Figure 15 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) without (blue and with Max exposure limit 75th, 50th, and 25th percentile (yellow, orange, red); Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & between exposure correlation of 0.5 vs 0 (independent)

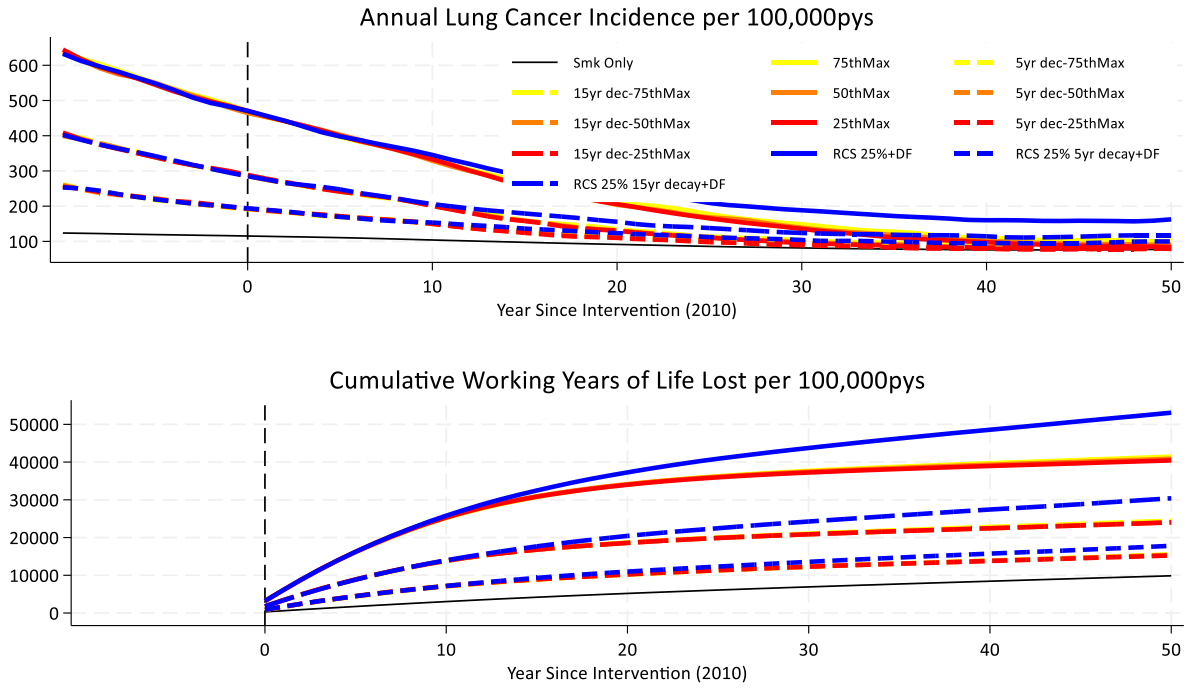


Table 16 - Relative Risks for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with 30%, 50%, and 75% reduced average exposure reduced vs Max Limit of exposure at 75th , 50th, and 25th percentile intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke, and intervention applied to both RCS & Diesel.

	Year since Intervention (2010)					
	0	10	20	30	40	50
15 year Half-life Decay						
Intervention - 30% Ave RCS & DF	1.00	0.99	0.93	0.91	0.90	0.88
Intervention - 75th Max RCS & DF	1.00	0.99	0.88	0.83	0.78	0.75
Intervention - 50% Ave RCS & DF	1.00	0.98	0.92	0.87	0.83	0.79
Intervention - 50th Max RCS & DF	1.00	0.98	0.84	0.80	0.73	0.70
Intervention - 75% Ave RCS & DF	1.00	0.99	0.89	0.85	0.79	0.78
Intervention - 25th Max RCS & DF	1.00	0.97	0.84	0.77	0.72	0.67
5 year Half-life Decay						
Intervention - 30% Ave RCS & DF	1.00	1.00	0.96	0.94	0.95	0.91
Intervention - 75th Max RCS & DF	1.00	0.99	0.92	0.91	0.88	0.87
Intervention - 50% Ave RCS & DF	1.00	0.98	0.94	0.91	0.91	0.88
Intervention - 50th Max RCS & DF	1.00	0.98	0.90	0.88	0.86	0.82
Intervention - 75% Ave RCS & DF	1.00	0.98	0.93	0.91	0.90	0.85
Intervention - 25th Max RCS & DF	1.00	0.98	0.89	0.86	0.83	0.79

Increasing the Pension Age to 70 years of age from 65

Not all interventions are a due to a planned concerted effort to modify workplace exposures. Certain policies, especially at governmental level can have consequences on workplace exposures despite not being the main focus of the policy. For example, increasing the pension age is a workplace intervention, that will likely increase exposure and subsequently risk. The final intervention proposed here is to increase the age of retirement from 65 years of age to 70. Currently all participants are assumed to retire at 65 if they do not develop lung cancer, or do not die before 65. Figure 16 illustrates the annual incidence rates and cumulative WYLL for the model with an increase to 70 (yellow) and without an increase (blue). Table 17 then reports the relative risk associated with the change for each of the follow up time points. As can be seen there appears to be no effect on Lung Cancer incidence. This is likely to be due to the average length of latency set to 30 years, and the exposure being experienced minor in comparison to the life-time of exposure already experienced.

Figure 16 - Annual Incidence Rates and Cumulative Working Years of Life Lost (pension age = 65) without (blue) and with increase in pension age to 70 (yellow); Smoking + RCS + Diesel Fumes model, with 25% RCS cumulative Relative Risk (%RR), and half-life decay (none, 15 year, and 5 year) & between exposure correlation of 0.5 vs 0 (independent)

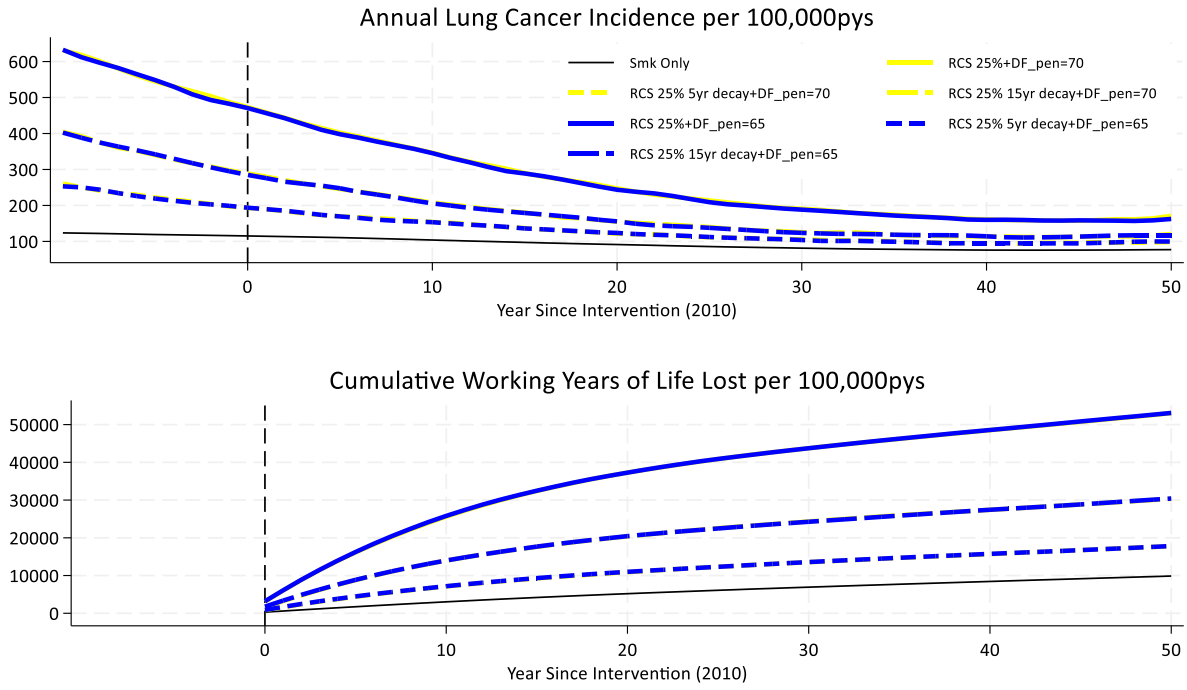


Table 17 - Relative Risks for five year average around 10 year follow up year post intervention (at 2010 = year 0) for Lung Cancer risk assocaited with pension age increase to 70 vs 65 intervention, in the Smoking + RCS model + Diesel Fumes model, where RCS percentage Relative Risk is 25% per unit increase and half-life decay in RCS exposure risk (15, and 5 year), and between exposure correlation = bespoke, and intervention applied to both RCS & Diesel.

	Year since Intervention (2010)					
Increasing Pension Age (70 vs 65)	0	10	20	30	40	50
Relative Risk - 15yr Half-life decay	1.00	1.02	1.00	1.01	1.00	0.99
Relative Risk - 5yr Half-life decay	1.00	1.01	1.01	1.02	1.00	0.99

Summary/Conclusions

To investigate Health Impact Assessment under complex exposomes, this study used simulations to first develop increasingly complex interrelating working life exposures, before investigating the performance of a set of exposure interventions on the health outcome. In order to ground the study in reality and make it relatable we attempted to replicate a simplified version the exposome associated with the construction industry between 1960 and 2020, namely exposure levels and trends in exposure for Respirable Crystalline Silica (RCS), Diesel Fumes, and Smoking. We then simulated a Lung Cancer health outcome whilst modifying the interrelationships between exposures and the health outcome, i.e. between-exposure correlations, decaying risk functions, latency periods, and the individual's exposure-outcome dose response relationship. We then applied a set of common interventions to exposures, ones that are often applied within health impact assessments for the construction industry. These included:

1. reducing the amount of exposure experienced, mimicking introduction of a new technology producing less exposure, or improved protective equipment.
2. Limiting the maximum exposure that can be produced, mimicking a new policy

These interventions were applied a single exposure (RCS) and both working life exposures (RCS and DF). A third intervention was also applied:

3. Increasing length of services within the industry by increasing pension age; mimicking introduction of government policies

The intervention effects were evaluated at the population level in a dynamic cohort of simulated construction workers in a simulated period representing calendar years 1960 to 2060. We compared the annual incidence rates, age of diagnosis, and working years of life lost during the period immediately after the intervention was set to occur (in this case this was set to 2010).

Once we ensured our simulated results were representative of the annual Lung Cancer rates i.e. approximately 120-110 per 100,000pys for the decade 2010-2020 and dropping from 130 per 100,000pys in the 2000s, we were able to apply our modifying exposome characteristics to better understand the influence on the annual incidence rate, and participant characteristics. Overall, we noted:

- Increasing the exposure-outcome relationship, along with the additive effects of additional exposures, both increase the risk of the outcome as would be expected. However they can be strongly tempered by other factors such as decaying risk factors (faster decay results in lower risk), and between exposures correlations, where increased strength of correlation reduces risk at the population level due pooling of exposures in fewer subjects.
- This highlights the difficulty in estimating a true exposure effect, when complex exposomes are present. Further, underlying trends in exposure, latency periods can also mask the true effects investigated in an observational study.
- Increased correlation between exposures seems to indicate small decrease in the annual incidence, possibly due to pooling of exposure in fewer but more highly exposed workers.

Possibly important to assess correlated exposures, to help target workers at higher risk of health effects.

- Multiplicative interactive effects within a cumulative exposure scenario can have strong effects on the annual incidence rate even when effects are perceived to be small.
- Decaying risk function, i.e. that the effect of any exposure experienced will dissipate over time, the more rapid the effect, the less influence the exposure will have on health outcomes, specifically those with a long latency. If then health outcomes have a short latency then the influence of the decay function becomes less prominent.

For health interventions:

- Firstly, increasing the Pension Age has no effect on workers risk, this is likely due to latency being on average 20 years therefore any increased exposure occurring at the end of working life will not affect an individual's risk until late in life i.e. in their 90s. Further to this, long term downward trends in exposure as defined in the study to replicate known exposure trends, mean working later in life will result in lower exposure than earlier in life, hence a minimal impact.
- We might expect the start of work to be more important, policies such as apprenticeships, or requiring further qualifications, may delay or reduce exposure in early life that might improve risk later on.
- We note, that max limit exposure tended to perform better than reducing the exposure level.
- However, reduction in exposure average and Max Exposure Limit have minimal effect in reducing risk. Particularly if the exposure-outcome effect is small.
- Partly due to delay caused by the lengthy latency period here requiring 20-30 years before an effect is seen particularly one large enough to see on annual risk. This was also affected by the long-term trends in exposure, reducing over time. This will likely mask some of the intervention effect where intervention is based on the exposure in the intervention year e.g. Max Limit of 75th percentile in 2010, may be the 50th percentile by 2020 or 2030 due to the trends also occurring not due to the intervention.
- We further investigated whether larger effect sizes will have substantial improvements in the health outcome. As would be expected, larger intervention size does reduce the risk of the outcome. However, the size of the improvement becomes increasingly minimal e.g. a Max limit of 25th percentile, appears to have little benefit over 50th percentile (diminishing returns).

Limitations

We acknowledge the study, specifically the simulations, could be limited in what they can achieve. Construction is one of the most widely investigated industries in terms of exposure assessment. Even so, it was very difficult to find accurate estimates of the exposure, across multiple job roles, over number of measurements occurring over long periods of time. We therefore had to make a number of assumptions related to exposure, exposure-outcome relationships. We believe they are as realistic as possible, but may be limited in nature. These include assumptions relating to:

- population average exposure levels
- trends in population average exposure levels from 1960 to 2020, and the assumption that these trends naturally stop in 2020 unless prompted by further interventions.
- variance parameters (between and within person variance), and the assumption that they do not change over time
- the assumption that everyone works (within this physically demanding manual job) until pension age if didn't develop LC or died
- assumes everyone works in the same job and their exposure only drops in line with population level trends
- interventions apply to all individuals in the study,
- interventions apply immediately after implementation
- assumes a linear-dose response relationship, does greater cumulative exposure increases have greater effects on the increased risk (are you more susceptible after a build up of exposure).
- Does exposure risk differ by age? Possible link to the cumulative exposure – response relationship?
- Does decay risk differ by age? Younger individuals may have more active clearence mechanisims than older participants.
- How exactly does the influence of multiplicative effects influence the annual incidence and the intervention effects
- Study doesn't account for multiple health events/competing risks (e.g. develop a respiratory illness), partly due to influence these would have on the exposure experienced, and the subsequent exposure outcome definitions we would need to determine.

Conclusion/future steps

This report serves as a summary of the results we have observed. Should anyone wish to explore the results in full, the results of this simulation study can be found in work-package 8s contribution to the EPHOR toolbox, in which we have included an interactive tool. Here they can be explored further by the user, who within the definitions outlined above can see for themselves the influence of an intervention effect under a modifiable exposome. We also provide the simulation code and set of programs that allow the user to define their own exposome characteristics, and intervention scenario.

This study aimed to generate a set of results that could be applicable within a variety of scenarios, however to make it relatable we have based this work on a construction site scenario using a set of atmospheric exposures and their influence on a single outcome. This means the results, despite our best intentions, are largely applicabable to the scenario and less generalisable that we had hoped. Further work would do well to build on our work to improve this aspect.

This might involve:

- Change in scenrio's
  - non-atmospheric ambient exposure, such as shit pattern work, or shorter bursts of work-related stress
  - Alterantive, more common, or non-binary (i.e. grade of severity) health outcome
  - Multiple health outcomes, with competiing risks, and their subsquent influence of the exposure levels
  - Acute exposure-response relationships rather than long latency periods
  - Dose-response relationshisp
  - Multiplicative effects of two, or more, exposures
  - Influence of secondary charateristics, such as sex, ethnicity, socio-deprivation on exposure response effects.

These may help further a more generalisable understanding of the influence of the exposme, and the impact of interventions within a wider number of settings.

Additionally, we currently have a number of methods that attempt to predict future burden of disease in a working population. These methods vary from the relatively simple use of Population Attributable Fractions to the more complex Age-Period-Cohort and G-methods. Some inconclusive work has been done to understand the accuracy of these methods in a practical setting when predicting future disease burden. This work we have propsed here would provide be a useful bases to apply these methods, and improve our understandng of our ability to accurately predict future disaese burden with and without health interventions.

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Appendix

A1 - Background Case studies/Literature Review

The following outlines a brief literature review of current work looking at RCS and Lung Cancer. This information will be used to simulate a representative cohort of construction workers and their exposome characteristics.

Literature review/Case Study - RCS and Lung Cancer

RCS (SiO2) comprises part of the earth's crust and thereby is one of the most common minerals in existence. It can exist in both an amorphous and crystalline form, of which the latter is the most stable and important. The respirable fraction of this crystalline form has been associated with a broad range of health symptoms including silicosis, respiratory disorders and disease and cancer.

In occupational settings, RCS exposure can commonly occur in scenarios where earth or earth products are processed or disturbed such as during mining, movement and cultivation of soul/earth (e.g. tunnelling, agriculture), when processing mined materials, producing or handling concrete, mortar etc, when sandblasting, in construction, in foundries as well as when manufacturing glass or ceramic products.

There is a breadth of epidemiological evidence related to the health effects of RCS and particularly in relation to lung cancer. Several meta-analysis have been published on the topic whereas in 1997 and more recently in 2018 IARC evaluated the carcinogenicity of RCS in the form of quartz or chistobalite (the most common forms of RCS).[37] Following their latest evaluation IARC experts concluded that there was sufficient evidence available that RCS in the forms of quartz or cristobalite dust causes lung cancer in humans and thereby classified RCS as a Group 1 carcinogen.

In their evaluation IARC reviewed studies on with the focus on exposure response relationship and included 10 cohort studies and 17 case-control studies, as well as 8 meta-analyses, of which though only one consider exposure-response relationships in its framework. From the cohorts included, 2 concerned exposure during work related to the diatomaceous earth industry, 4 during ore mining, 2 during quarrying, and 2 during the processing of sand and gravel. From those studies Checkoway et al.[38] and Rice et al.[39] studies the association between cumulative exposure to RCS and lung cancer among 2342 workers in a diatomaceous earth mining and processing facility in California initially by applying analysis with exposure treated both as a categorical and continuous variable. Their analyses with a continuous exposure variable returned a significant positive association between cumulative RCS exposure and lung cancer with a RR (95CI%) of 1.06 (1.01 – 1.11) in the first analysis and 1.64 for the re-analysis following implementation of a 10 year lag.

Steenland and Brown,[40] used quantitative estimates of cumulative exposure based on particle counts to study the association between RCS and lung cancer in a population of more than 3000 US miners. The authors found no obvious evidence for an exposure–response relationship with lung cancer mortality. This is in contrast to the results of a cohort of 2209 South African gold miners by Hnizdo and Sluis-Cremer published a little earlier.[41] In this cohort the authors calculated the cumulative respirable surface area years for the participants and in models with a continuous a exposure there was a significant association with the incidence of lung cancer (RR=1.02; 95%CI = 1.01-1.04). Similarly, a cohort of 724 Sardinian miners with silicosis using quantitative estimates of cumulative exposure to RCS and radon categorised in 4 intensity groups also showed the potential presence of an association between RCS and lung cancer mortality with SMR between 1.25 and 1.55.

However, there was no evidence for an exposure-response relationship and tests for trends remained non-significant.[42]

Similar results were obtained in a study of 440 German stone and quarry workers but among Attfield & Costello analysed quantitative RCS dust measurements undertaken throughout a study of 5414 granite quarry and shed workers and estimated the cumulative exposure of the participants.[43] They used the derived estimates to study the association with lung cancer mortality and observed a clear trend of an increased risk of lung cancer mortality with increasing cumulative respirable exposure. Risk estimates ranged between 1.18 and 2.6 in analysis utilising 7 groups of exposure (0.25,0.5,1.0,1.5, 2.0, 3.0, 6.0) versus the non-exposed.

In another cohort involving 4626 industrial sand workers employed between 1960 and 1988 in 18 sand and gravel companies, Steenland & Sanderson also employed quantitative estimates of exposure and reported indications for an exposure-response relationship with lung cancer mortality.[44] Estimates of Risk were 0.78, 1.51 and 1.57 for those subjects with >0.10-0.51, >0.51-1.28, and >1.28 mg-yrs/m3 of exposure compared with those with cumulative exposure ranging between >0-0.10 who were the reference. Brown & Rushton also studies the association of cumulative RCS to lung cancer in a cohort of workers from the sand industry.[45 46] In this case though, the RR appeared to increase in the first two quartiles (RR =1.24 and 2.42, respectively), but fell below 1.0 in the highest quartile (RR=0.88). As a result no trends in the exposure-response relationship were observed.

Among case-control studies Reid and Sluis-Cremer in a study of 159 miners and 318 aged matched controls nested within a larger cohort of South African gold miners observed an OR (95% CI) of 1.19 (0.97-1.70) when analysing estimates of the participants cumulative RCS exposure as a continuous variable.[47] Similar evidence for a positive exposure-resposne relationship were also reported in another study of South African gold miners including 78 cases and 386 controls.[48] The authors observed an increasing trend with increased cumulative exposure significant for the highest exposed category compared to the lowest. The derived ORs were 1.83 (0.8-4.1), 1.85 (0.8-4.3) and 3.19 (1.3-7.6) for the mediate (2.7-4.3 mg-yr/m3), intermediate (4.4-6.3 mg-yr/m3) and high (>6.3 mg-yr/m3) exposure group compared to the lowest (0<2.7 mg-yr/m3), respectively.

Cherry et al., in a study of 52 males cases and 197 male controls employed in the ceramics (i.e. pottery, sandstone, refractory) industry used continuous quantitative estimates of cumulative RCS dust exposure (µg-yr/m3) and of average intensity to study the exposure response relationship with lung cancer.[49] The authors observed an OR of 1.01 (0.85-1.19) in the analysis using cumulative exposure and of 1.67 (1.13-2.47) in the analysis using the average intensity concentrations.

Similar positive trends in exposure response relationships were also observed in two case-control studies of workers in the sand and gravel industry. First Steenland and Sanderson in a study of 75 cases and controls nested within the previously mentioned cohort reported evidence of exposure–response using quartiles of cumulative exposure (p = 0.04), but the evidence were much stronger when average intensity was used with OR estimates ranging between 0.92 and 2.26 (p = 0.003).[44] The ORs for the cumulative exposure when lagged 15 years ranged between 1.35 to 2.0. Similarly, MacDonnald et al., in a study of 105 cases matched with up to 2 controls each on the basis of age and date of first employment reported OR of 1.10 , 1.77, and 2.64 for the cumulative RCS exposures ranging between 700 – 1800, 1800-4500, >4500 ug-yr/m3 compared with lowest exposed who had levels of cumulative exposure <700 ug-years/m3.[50] Further evidence and similar results on the exposure response relationship between RCS exposure and lung cancer were also provided in case control studies among Chinese iron and steel workers and US aluminium foundry workers.[51 52]

Steenland et al. performed a nested case-control analysis of a pooled study comprised from ten cohorts representing various countries and industries.[53] The analysis comprised of 992 cases and 100 controls per case matched upon race, sex, date of birth and study. Indices of exposure employed included quantitative estimates of average and cumulative RCS exposure at a normal and log scale with and without lags. The authors reported highly significant trends with lung cancer risk ($P < 0.0001$) for all cumulative indices employed. Reported OR for the cumulative RCS exposure (unlagged) ranged between 1.0 – and 1.6.

Another meta-analytical study reporting results on the exposure-response relationship between was published by Lacasse et al.,.[23] Based on 10 studies (4 cohort and 6 case–control studies) having quantitative RCS measurements of exposure and including adjustments for smoking the authors observed an increasing risk of lung cancer with increased cumulative RCS exposure. RRs corresponding to increases of 1.0 and 6 mg/m3 per year were estimated to be 1.22 (CI: 1.01–1.47) and 1.84 (CI: 1.48–2.28), respectively.

Finally, m recently Shabhazi et al., published a meta-analysis looking on the relationship between RCS and the risk of developing lung cancer in studies published as recently as 2020.[23] Nineteen studies from 14 countries were included. Using random effect analysis with linear and cubic spline effects the authors observed a significant linear association between RCS exposure and risk of lung cancer with a RR of 1.25 and a 95% CI between 1.03 and 1.49, which suggested an increase of 25% in risk of lung cancer per unit of increase in cumulative exposure to RCS.

A1.2 – Background Summary stats for Lung Cancer Incidence by Country

Table A1 - Estimated Lung Cancer incidence by country - summary

Estimated incidence by country - summary Both sexes, Lung, All ages, 2020 to 2020				
Country	Number of cases	Crude rate	ASR (European new)	Cumulative risk
Austria	5256	59.8	58.1	6.2
Belgium	9646	81.6	83.5	9
Bulgaria	4300	61.6	55.7	5.4
Croatia	3235	77	72.6	7.6
Cyprus	571	47.3	60.2	6.7
Czechia	6560	61.6	60.8	6.8
Denmark	5047	87.4	86.3	9.8
EU-27	318327	71.4	67.3	7.2
Estonia	809	63	60.3	6.6
Finland	2935	52.2	47.7	5.6
France	48299	71.4	71	7.4
Germany	64804	80.4	67.7	7.3
Greece	8960	83.7	76	8.2
Hungary	10274	104.8	101.7	10.2
Ireland	3271	71	91.1	10.8
Italy	41953	67.7	59.3	6.8
Latvia	1205	64.1	60.1	6.9
Lithuania	1500	56.2	51.9	5.7
Luxembourg	351	55.5	68	8
Malta	258	58.9	56.3	6.9
Netherlands	13500	78.8	76.6	8.6
Poland	29509	76.9	80.1	8.6
Portugal	5415	53.4	47.4	5.2
Romania	12122	61.6	62.3	6.3
Slovakia	3316	61.2	66.4	7
Slovenia	1476	70.7	66.5	7
Spain	29188	63.7	61.2	6.4
Sweden	4567	45	43.9	5.3

A2 – Background the Co-exposure Smoking:

Smoking is a significant risk factor for lung cancer, being associated with smoking since the early 1950s and now widely agreed to be a causal in relationship. The International Agency for Research on Cancer (IARC), who classifies the role of smoking in cancer development, considers 72% of lung cancer cases in the UK to be caused by smoking - 71% by active smoking, and 1% by environmental tobacco smoke.[54] The risk associated with lung cancer increases with both smoking duration, amount and age of initiation[55-57]. Of the three, duration appears to be most influential with smoking one pack of cigarettes a day for 40 years being more hazardous than smoking two packs a day for 20 years[58 59]. Exposure however shows a strong dose response effect, as compared to those who never smoked, Lung cancer risk has been observed to be approximately 5 times higher in people who

smoke of 1-4 cigarettes per day, 12 times higher for 8-12 cigarettes per day; 24 times higher for 25+ cigarettes per day; and 39 times higher in people who smoke 42+ cigarettes per day[55 60-62]. In a 2000 UK study of national trends in smoking since 1950 the cumulative risk of lung cancer by age 75 in a group of smokers who smoked throughout most of their adult life was 15.9% for men and 9.5% for women.[56] The cumulative risk by 75 years of age were 9.9%, 6.0%, 3.0%, and 1.7% for those who stopped smoking around 60, 50, 40, and 30 years of age.

Cumulative smoking exposure is commonly measured in terms of pack-years. Pack-years is defined as the average number of cigarettes smoked per day multiplied by the duration of smoking in years, and then divided by 20 (cigarettes per pack). Based on the Annual Population Survey, The office for national statistics (ONS) reports statistics on the proportion of never smokers, smokers who have quit, current smokers, and their average daily cigarette smoking in the general population by gender and age group since 1974.

(https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/datasets/adultsmokinghabitsingreatbritain). This indicates the proportion of never smokers has increased from approximately 30% in the 1970s, to 55% in the 2010s. Those who have reported quitting have increased from 35% to 60%, and current smokers dropped from 47% to 18%. The average number of cigarettes per day has also dropped from 18.5 to 11.7, with the biggest drops occurring post 2010. Note, by age groups the proportion of current smokers was highest in those aged 25-34, indicating that most start smoking in their early 20s.

In terms of construction workers, Claessen et al (2010) reported on Smoking habits and occupational disability in a cohort of 14 483 construction workers in Württemberg, Germany.[63] Twenty-four percent were never smokers, 18% former smokers, 21% light or moderate smokers (1–19 cigarettes/day or equivalent), and 37% heavy smokers (>=20 cigarettes/day). The European Community Respiratory Health Survey (ECRHS) reported prevenance of smoking in male construction workers across 14 European countries in 1992 at 53.7%.[64] The ECRHS and it follow up study ECHRS 2, reported smoking prevalence of smoking across all countries had dropped 8 years later by 5%.[65] Preller et al, assessing male lung cancer risks for industrial sectors in the Netherlands.[66] They reported for lung cancer cases and healthy workers, the average daily cigarette smoking was 19.7 (SD10.8) and 17(SD10.6), and the mean duration in years was 41.2 (SD 9.1) and 33.5 (11.8), respectively. In terms of pack-years, Consoni et al studied lung cancer among bricked layers within the Synergy pooled case-control study.[67] The mean pack-years of cigarette smoking was 45.2 (SD 28) in the lung cancer cases and 23.3 (SD 24) for the controls. Across all the case-control studies from between 1985-2010 the bricklayers 2.2% were reported as never smokers, 34% former smokers, and 64% current smokers.

Remen et al., assessed the relations between lung cancer and various smoking metrics, including duration, daily intensity, time-since cessation pack-years in a population-based case-control study of all lung cancer cases for males and females aged 35–75 years residing in Montreal.[68] For pack-years categories: OR for 0-20 pack-years=1.3 (0.67-2.66), 20-40 PY OR=3.99 (2.21 - 7.19), 40-60 PY OR=9.46 (5.38, 16.6), 60-80 PY OR=13.14 (7.3-23.6), 80-100 PY OR=11.13 (5.74-21.56) and +100 PY OR=23.64 (12.87-43.4). When they presented the adjusted OR for continuous cumulative smoking (pack-years) and lung cancer risk the OR (95% CI) = 2.87 (2.35 - 3.52), meaning that every additional pack-year increased the lung cancer resulted in an approximately 3 fold increase in risk. Dement et a. looked for risk prediction of a pack-years increase in construction workers with a mean (SD) pack-years of 21.7 PY (SD 25.9) for 20.3% current and 45.6% former smokers.[69] In contrast to Remen et al., found for each additional pack-year of cigarette smoking increased lung cancer mortality risk even after

model adjustment for smoking status (HR=1.006, 95% CI 1.002 to 1.010). However, this model adjusted for current smoking status (who were at increased risk of HR=24.3 time the never smokers) and so is not the total effect of pack-years. Mean pack-years here was 21.7 PY (SD 25.9) where 20.3% were current smokers and 45.6% ex-smokers. Lubin and Caporaso investigated pack-years in terms of smoking intensity.[59] At higher smoking intensity, they found that the excess odds per additional pack-years of smoking were lower than for lower smoking intensities. The excess odds ratio per pack-years were reported at 0.293, 0.315, 0.247, and 0.203 for groups defined as <20, 20–29, 30–39, and ≥40 cigarettes per day, respectively. Vlaanderen et al. explored effect modification of the association of cumulative exposure in pack-years of cigarette smoking and cancer risk by intensity of exposure (no cigarettes) and time since cessation.[70] With respect to intensity and pack-years of cigarette smoking they observed a negative effect modification for persons who smoked more than 20–30 cigarettes per day. Even so, the excess odds ratio associated with per pack-years of 0.3-0.4. Indicating an odds ratio associated with 1 pack-year increase of 1.3-1.4.

In addition to a review of the literature, empirical modelling using the SYNERGY dataset by members of the EPHOR team indicated that there was a RR for lung cancer of 1.123 (95CI: 1.118-1.128) for each additional pack-year of cigarette smoking. This was using a decay function of T1/2=10 year (meaning that exposure from 10 years ago accounts for half of exposure today). This 10 year half-life decay reported the best fitting model. This SYNERGY dataset is the same for developing decaying risk functions for other exposures within EPHOR.

A3 - Background to Diesel Fumes aka Elemental Carbon

Lewne et al., reported diesel fumes in the form of Inhalable Elemental Carbon (EC) among Swedish construction workers to average between 4 ug/m^3 for outdoor construction work and 87 ug/m^3 during tunnel construction.[71] Levels of respirable exposure among workers involved in tunnel construction work in the area London were reported to have a GM level of 18 ug/m^3 with a GSD of 1.0 which was generally similar to the levels of exposure reported among Canadian underground workers recently (GM= 13.2 ug/m^3; GSD=1.83).[26 72] In the same study among Canadian construction workers measurements of EC during below ground and above ground work had GM (GSD) levels of 3.56 ug/m^3 (1.94) and 1.49 ug/m^3 (1.75), respectively. This study was performed between 2018 and 2020 and the measurements had an overall GM of **3.71 ug/m^3** with a GSD of 3.32.[26] Time trends in occupational fume and dust exposures have previously been reported to range from -19 to approximately 4%.[73] A more recent study modelling historical occupational exposures to diesel using elemental carbon as the exposure indicator estimated that the levels of exposure among off road machinery operators reduced from approximately 90 ug/m^3 in the mid 1970's to approximately 10 ug/m3 in mid 2000s that corresponds roughly to an annual reduction of 3%. Modelled exposure estimates suggested even stronger reductions to have occurred during the same period (1970 to 2004) for city bus drivers (from 140 ug/m3 to 20 ug/m^3) and garage workers (from ~100 ug/m3 to ~10 ug/m^3). Accounting for the earlier reported results among Canadian workers and assuming a log normal exposure distribution with a 3% annual decline in exposure to have occurred following 1970 and a 40 years career with exposure with beginning in 1970 we estimate an average annual exposure for the workers of 9.540 ug/m^3 and a total cumulative exposure estimate for the period of 381.58 ug/m^3 *years. As with RCS, for our simulations we will assume that no reductions in exposure have occurred prior to the year 1970 (i.e. exposures were constant during this period) to avoid potential occurrence of unrealistic estimates.

A4 – Mini-Simulation study – Within vs Between Variance

Within and Between person annual exposures – Simulation Study

Background:

Exposure measurements, such as within the construction industry, are typically measured on a daily basis resulting in daily averages and daily estimates of `within' person and `between' person variation. Repeated measurements are not typically taken/reported over a period of several years, meaning population averages, and within and between person variation is often not available for the annual average of exposure estimates.

In our study simulating annual exposures over a lifetime, we are currently using `within' and `between' person variance statistics based on these `daily' measurements to then simulate `annual' average exposures of silica, diesel, and smoking over a period of several decades. The mismatch in the daily vs annual exposures results in likely overestimated within and between variance parameters and correspondingly overestimates in the simulated exposures for individuals within our study compared to a more realistic scenario.

Additionally, the cumulative exposure estimates are traditionally calculated using an arithmetic annual mean. Here we simulate daily exposure estimates based in the Geometric Mean and standard deviation (sd), and then calculate the Arithmetic Mean to inform the cumulative exposure simulated in the main study.

Methods

To improve our estimates in the main study, we have performed a small simulation study prior to the main study in which the daily exposures for smoking, silica, and diesel are simulated. These were simulated based on the daily averages, between person, and within person standard deviations, as proposed within the main study for the years 1960 to 2020. In other words the three exposures are simulated assuming a log normal distribution such that:

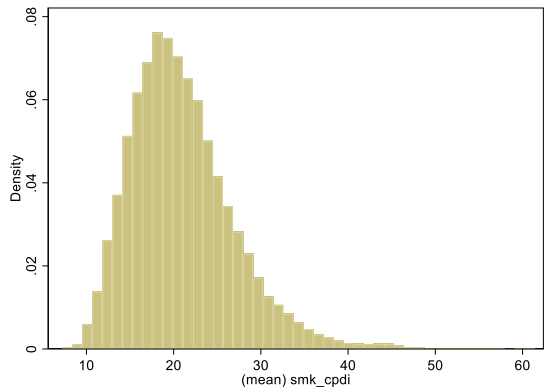
- Smoking daily averages were assumed to drop by 1 cigarette per decade from 18.5 cig per day in 1960, and have a within person sd = 2 and between person sd = 5
- Silica daily averages were assumed to drop from 0.238 mg/m3 in 1960 to 0.015 mg/m3 in 2020, and have a within person sd = ln(2.17) and between person sd = ln(1.7)
- Diesel daily averages were assumed to drop from 15.308 ug/m3 in 1960 to 3.887 ug/m3 in 2020, and have a within person sd = ln(2.65) and between person sd = ln(1.43)

For 1000 individuals each daily exposure were simulated (workplace exposures set to zero for weekends, and 30 days for holidays) from 1st Jan 1960 to 31st Dec 2019, then collapsed to the average exposure for the year, and calculated the between and within person variance/sd for each of the three exposure periods. This was repeated for 1000 replications, so 1,000,000 individuals in total.

Results

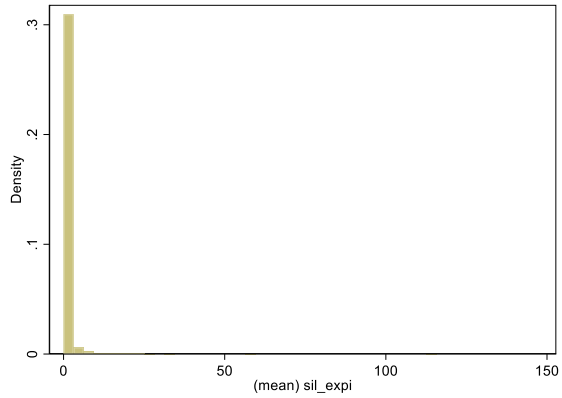
Example annual exposure distributions from 1000 individuals over 50 years

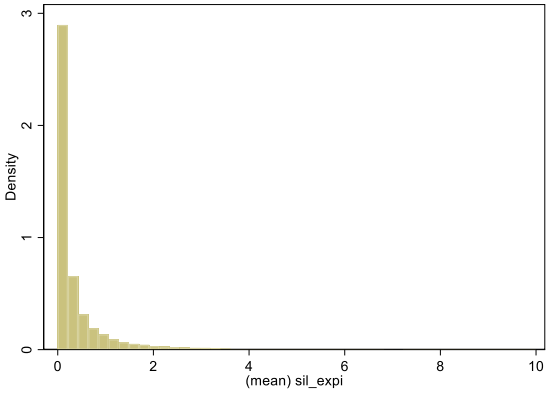
Smoking (cpd) – Annual Average Cig per day (1960-2020)



Variable	N	Mean	SD
smk_cpdi60	1000	22.29109	.1912867
smk_cpdi65	1000	22.29073	.1922167
smk_cpdi70	1000	22.2904	.1913648
smk_cpdi75	1000	22.29075	.1917838
smk_cpdi80	1000	21.21447	.1822839
smk_cpdi85	1000	21.20445	.1819094
smk_cpdi90	1000	20.13036	.1727458
smk_cpdi95	1000	20.11831	.1731172
smk_cpdi00	1000	19.04721	.1633066
smk_cpdi05	1000	19.02884	.16354
smk_cpdi10	1000	17.96114	.154736
smk_cpdi15	1000	17.93936	.1545197

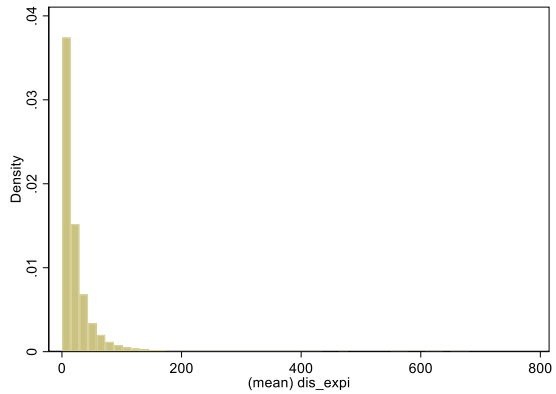
Silica (mg/m3) – Annual Average exposure per day (1960-2020)

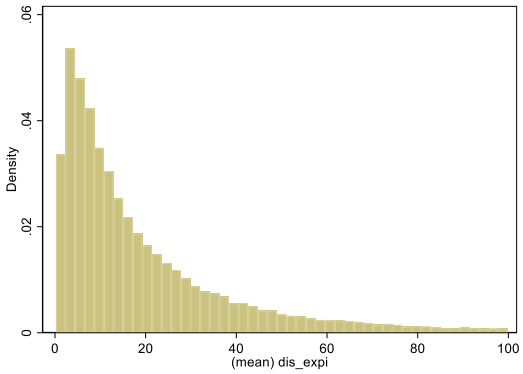




Variable	N	Mean	SD
sil_expi60	1000	.404368	.019449
sil_expi65	1000	.4043748	.0194558
sil_expi70	1000	.4043852	.0194417
sil_expi75	1000	.2962895	.0142518
sil_expi80	1000	.2181061	.0104999
sil_expi85	1000	.1606183	.0077266
sil_expi90	1000	.1177481	.0056666
sil_expi95	1000	.0870862	.0041903
sil_expi00	1000	.0632462	.0030411
sil_expi05	1000	.0461763	.0022218
sil_expi10	1000	.0342206	.0016467
sil_expi15	1000	.0256727	.0012359

Diesel (ug/m3) – Annual Average exposure per day (1960-2020)





Variable	N	Mean	SD
dis_expi60	1000	23.26912	.7776328
dis_expi65	1000	23.26971	.7780433
dis_expi70	1000	23.26783	.7783843
dis_expi75	1000	20.00063	.6695773
dis_expi80	1000	17.1814	.5736812
dis_expi85	1000	14.7591	.4937162
dis_expi90	1000	12.67787	.4239087
dis_expi95	1000	10.89096	.3642656
dis_expi00	1000	9.355369	.3128051
dis_expi05	1000	8.035908	.2688014
dis_expi10	1000	6.902316	.2307904
dis_expi15	1000	5.929757	.1982208

Within/Between Variation (of 1000 replications of 1000 individuals)

sd = standard deviation (arthmetric version); gsd = geometric standard deviation
_b_ = between person ; _w_ = within person

Smoking (cpd) – Annual Average Cig per day (1960-2020)

```
   Variable |         N      Mean        SD
------------+----------------------------------
    smk_b_sd |      1000  5.728628  .1617871
    smk_w_sd |      1000  1.025218  .0120964
   smk_b_gsd |      1000  1.303599  .0077264
   smk_w_gsd |      1000  1.043559  .0001238
-------------------------------------------
```

Silica (mg/m3) – Annual Average exposure per day (1960-2020)

```
. tabstat sil*, stat(N mean sd) col(stats)

    Variable |         N      Mean        SD
-------------+----------------------------------
    sil_b_sd |      1000   1.56974  .7512485
    sil_w_sd |      1000  1.245786  .5902841
   sil_b_gsd |      1000  4.493232  .1564008
   sil_w_gsd |      1000  1.192406  .0003387
```

```
YELLOW BASED ON DANISH = DAILY GSD BW = 5.98 / WW = 2.71
GREEN BASED ON DUTCH = DAILY GSD BW = 3.20 / WW =2.16

Starting values split into 4.5/2.4
```

Diesel (ug/m3) – Annual Average exposure per day (1960-2020)

```
. tabstat dis*, stat(N mean sd) col(stats)

    Variable |         N      Mean        SD
-------------+----------------------------------
    dis_b_sd |      1000  33.74559  5.075175
    dis_w_sd |      1000    15.182  2.243138
   dis_b_gsd |      1000  2.800965  .0641414
   dis_w_gsd |      1000    1.1048  .0002466
-------------------------------------------

YELLOW BASED ON DANISH = DAILY GSD BW = 2.71 / WW = 1.94
GREEN BASED ON DUTCH = DAILY GSD BW = 2.85/ WW = 1.79

Starting values split into 2.8/1.8
```

Note, between persons in themselves do not change here. smk_b_sd = 5.74 is a little different from 5, but I believe this is due to trying to summarise arithmetic parameters on data that is here geometric i.e. log-normal.