The relationship between particulate matter and lung cancer a systematic review

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Abstract:
In this review we investigated the relationship between particulate matter(PM) and lung cancer in western countries.
Pubmed and embase were systematically searched for cohort studies concerning lung cancer and PM. 23 cohort studies met all our inclusion criteria. In these 23 cohort studies there were 30 analysis performed examining PM and lung cancer. There was a significant positive correlation between PM and lung cancer mortality/incidence in 14 out of the 30 analysis.
Four analysis show a negative (non-significant) correlation, while all the remaining show a positive non-significant correlation. These negative correlations are not major.
In the discussion, the differences in the cohort studies are examined in terms of measurement methods of PM, timing and confounders.
There is also a brief discussion of indoor pollution, causality and PM as a collective noun.

In conclusion, there is a clear trend towards a positive association between PM and lung cancer. Considering all the studies to date, the link between PM and lung cancer is clear.

More research is needed, especially to find effective solutions to these problems, such as pollution reduction and indoor ventilation.

Introduction:
As Belgian primary care workers we are interested in the relationship between air pollution and the health effects on our patients. In this review we focus on the potential relationship between particulate matter(PM) and lung cancer in western countries.

lung cancer is the leading cause of cancer death and the second most commonly diagnosed cancer.[1] Lung cancer has, despite treatments, an overall poor prognosis, therefore prevention should be key.

Air pollution has its negative health effects. The WHO calls it one of the greatest environmental risks to health.[2]It is known that high concentrations of air pollution are hazardous to our health and now studies show low levels of exposure also cause harm[3]. (this applies to PM)The suspected annual years of life lost globally is 233 million per year with the following distribution. It causes a loss of life expectancy(LLE) that is comparable to that of tobacco smoking.[4]This loss of life expectancy is not only based on lung cancer mortality and has for example also cardiovascular disease and lung diseases such as COPD as contributors.[5,6] This shows that PM is to be seen in a context further then only lung cancer.

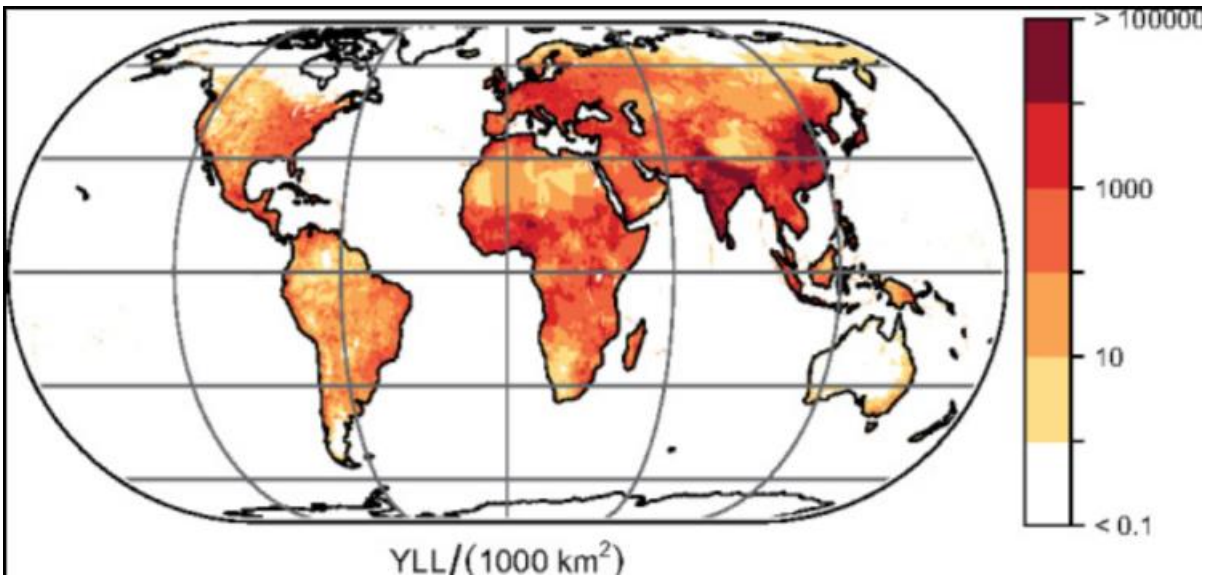


Figure 1: Years of life lost from air pollution visually shown on world map. Figure copied from Lelieveld et al.[4](Years of life lost from air pollution visually shown on world map. Adapted from "Loss of life expectancy from air pollution compared to other risk factors: A worldwide perspective." By Lelieveld et al. 2020, Cardiovascular Research, 116(11), 1910–1917)

Figure 1 shows the years of life lost due to air pollution visually on a world map. Worldwide, 233 million years of life are lost each year.[4]
PM refers to the sum of all solid and liquid particles suspended in air.[7]
There are two groups where the PMs can be divided in, namely PM 2.5 and PM 10. As shown in figure 1 PM2.5 is particulate matter smaller than 2.5 µM and PM10 is particulate matter smaller than 10 µM.

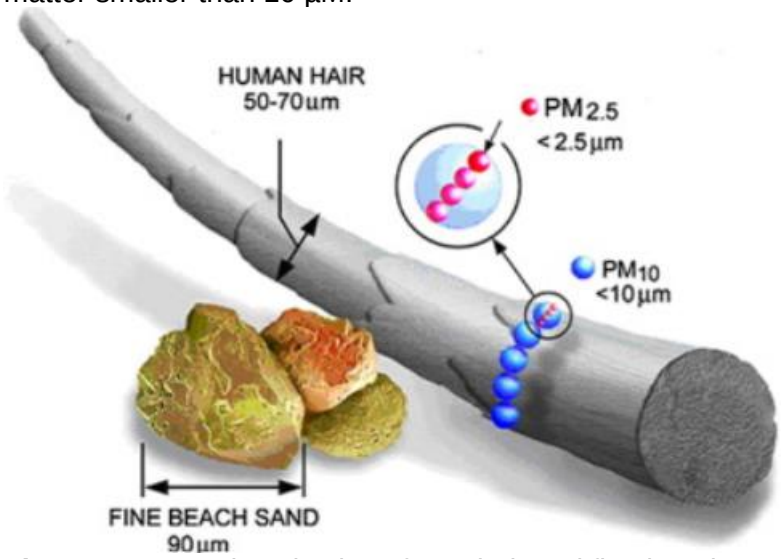


Figure 2 Comparison in size of PM, hair and fine beach sand. Figure copied from Guaita et al. [8] (Comparison in size of PM, hair and fine beach sand. Adapted from "A review on the human health impact of airborne particulate matter," by Guaita et al., 2011, Int J Environ Health Res., 21:4, 260-274)

PM is a collective name for multiple particles. This variety of particles makes it harder to examine because the effects can vary since we are not always studying the same particles. The composition of particulate matter in the two size classes is highly variable and depends on local geographic and meteorological conditions, as well as specific sources of PM, such as construction work, unpaved roads or nearby deserts, which contribute to high levels of particulate matter.[3] Many other substances like NO2 and SO42 might have an association with lung cancer but we chose to put our focus on PM.
Earlier studies already found a significant increase in lung cancer mortality and incidence associated with PM.[3,9] None of these seem to put their focus purely on western studies. Since we want to know the relevance for the Belgian population, we chose to put our focus on western studies. Cohort studies will be the preferred study design because of their high quality of evidence and large sample sizes.

Methods:

We performed a systematic review.
Embase was searched for relevant studies up to January 2022.
Pubmed was searched for relevant studies up to October 2022
Our selection criteria were:

- Key words title and abstract.
- Studies originating from western countries.

- Language should be English/ Dutch
- Only cohort studies
- Examines PM and lung cancer
- PM 2.5 and PM 10
- Incidence/ lung cancer mortality
- Outdoor air pollution

Our search strategy for Embase is the following:

('particulate matter'/exp OR 'particulate matter' OR 'particulate matter 2.5'/exp OR 'pm2.5' OR 'fine particulate matter' OR 'inhalable fine particles' OR 'inhalable particles pm2.5' OR 'particulate matter 2.5' OR 'particulate matter 2.5 micrometers' OR 'respirable fine particles' OR 'respirable fine particulates' OR 'respirable particle fraction pm2.5' OR 'fine dust' OR 'fine particle'/exp OR 'pm10' OR 'particulate matter 10') AND ('lung cancer'/exp OR 'cancer, lung' OR 'lung cancer' OR 'pulmonary cancer' OR 'schneeberg disease' OR 'non small cell lung cancer'/exp OR 'bronchial non small cell cancer' OR 'bronchial non small cell carcinoma' OR 'carcinoma, non-small-cell lung' OR 'lung cancer, non small cell' OR 'lung non small cell cancer' OR 'lung non small cell carcinoma' OR 'non small cell bronchial cancer' OR 'non small cell cancer, lung' OR 'non small cell lung cancer' OR 'non small cell lung carcinoma' OR 'non small cell pulmonary cancer' OR 'non small cell pulmonary carcinoma' OR 'non-small-cell lung carcinoma' OR 'pulmonary non small cell cancer' OR 'pulmonary non small cell carcinoma' OR 'small cell lung cancer'/exp OR 'bronchial small cell cancer' OR 'bronchial small cell carcinoma' OR 'lung small cell cancer' OR 'lung small cell carcinoma' OR 'microcellular lung carcinoma' OR 'pulmonary small cell cancer' OR 'pulmonary small cell carcinoma' OR 'small cell bronchial cancer' OR 'small cell bronchial carcinoma' OR 'small cell cancer, lung' OR 'small cell lung cancer' OR 'small cell lung carcinoma' OR 'small cell pulmonary cancer' OR 'small cell pulmonary carcinoma' OR 'malignant lung tumor')

Our search strategy for pubmed was the following:
((("Particulate Matter"[Mesh]) OR "Dust"[Mesh] OR "Fine Dust" OR "particulate matter 2.5" OR "inhalable fine particles" OR “inhalable particles pm2.5” OR “particulate matter 2.5 micrometers” OR "respirable fine particles" OR "respirable fine particulates" OR "fine particle"OR “PM10” OR “particulate matter 10”)) AND ("Lung Neoplasms"[Mesh] OR "Small Cell Lung Carcinoma"[Mesh] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR “Schneeberg disease”)

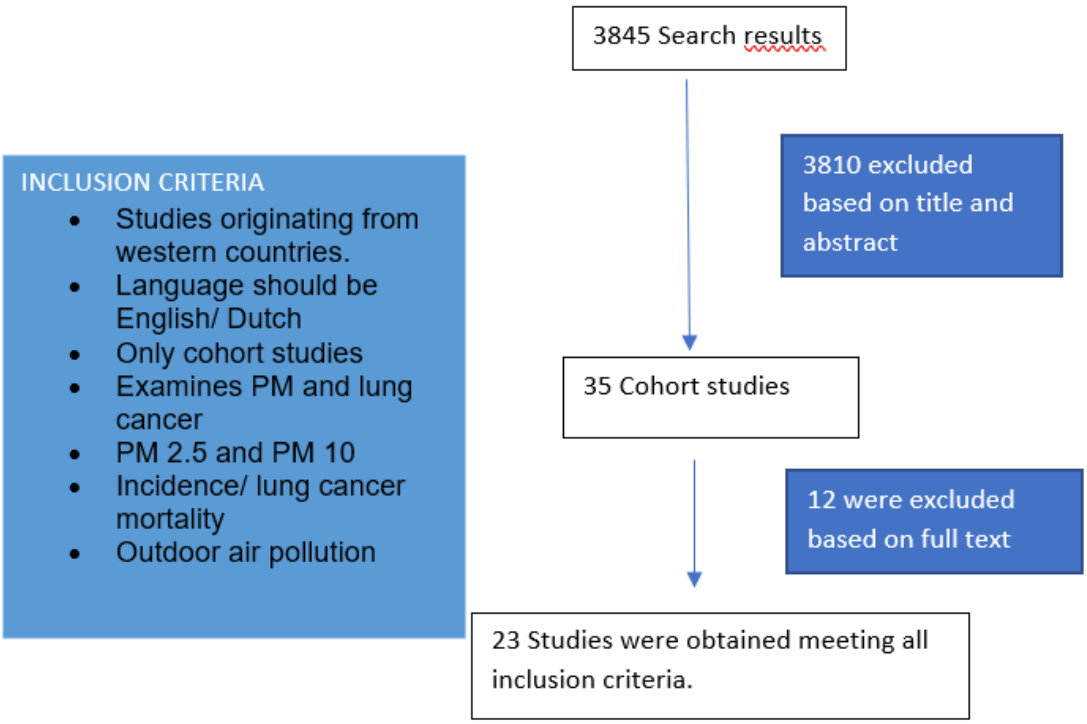


Figure 3: Search strategy

Data extraction:

The following data points were extracted:

- Hazard ratio (HR) or Odds Ratio
- Measurement method/prediction model of PM concentrations
- Population
- Which PM and lung cancer mortality or incidence
- Correction for smoking

Results:

Table 1 and 2 below are a representation of all studies found reviewing the literature.

For every study we incorporated the hazard ratio, subject researched, measurement method of PM, population and adjustments for the hazard ratio.

There are different ways of measuring the particulate matter exposure. For example residual interpolation optimised for ozone-Immission Frequency Distribution Model (RIO-IFDM) and Hybrid-land use regression are both based on air pollution monitoring data, satellite air pollution data and take into account traffic line sources. While other studies are only based on ground monitoring data.

Study	Hazard ratio(95% CI)	Measurement method PM	Population	Subject researched	Adjustments HR
Bauwelinck et al., 2022[10]	0.983 (0.950 - 1.017)	Hybrid Land Use Regression (LUR)	5 million adults followed for an average of 9.97 years	PM2.5 AND lung cancer mortality	Indirectly adjusted for smoking and BMI using surveys.
Bauwelinck et al., 2022[10]	1.031 (0.994 - 1.070)	RIO-IFDM	5 million adults followed for an average of 9.97 years	PM2.5 AND lung cancer mortality	Indirectly adjusted for smoking and BMI using surveys.
Klompmaker et al., 2021 [11]	1.046 (1.033 - 1.060)	national land-use regression (LUR) Europewide hybrid and dispersion models.	10.5 million adults were followed from 1 January 2013 to 31 December 2018.	PM 2.5 AND lung cancer mortality	Indirectly adjusted for smoking using a method created by Shin et al.[12]
Klompmaker et al., 2021 [11]	1.024 (1.012 - 1.036)	with national land-use regression (LUR), Europewide hybrid and dispersion models.	10.5 million adults were followed from 1 January 2013 to 31 December 2018.	PM 10 AND lung cancer mortality	Indirectly adjusted for smoking and BMI using a method created by Shin et al.[12]
Hvidtfeldt et al., 2021[13]	1.19 (1.11 - 1.28)	Europe-wide hybrid land use regression (LUR) models	306,104 individuals with 5.541.672 person-years of follow up.	PM2.5 AND lung cancer incidence	Adjusted for smoking

Hvidtfeldt et al., 2021[14]	1.21 (1.11 - 1.31)	Europe-wide hybrid land use regression (LUR) models	307,550 cohort participants, during a mean follow-up of 18.1 years.	PM2.5 AND lung cancer incidence	Adjusted for smoking
Coleman et al., 2020[15]	1.13 (1.00–1.26)	Each study subject was assigned pollution exposure based on estimated modeled population-weighted average concentrations of PM2.5 at their resident census tract, averaged across the 17-year period from 1999 through 2015	635,539 individuals surveyed from 1987 to 2014	PM 2.5 AND Lung cancer mortality	Adjusted for smoking
Chang et al., 2020[16]	1.07 (0.90 - 1.26)	Using previously validated spatiotemporal models[17–19] based on ground monitoring data	97,303 women from 1994 through 2010	PM 2.5 AND lung cancer incidence	Adjusted for smoking
Bauleo et al., 2019[20]	1.10 (0.92 – 1.33)	Lagrangian particle dispersion model called SPRAY using emission parameters from 1988	71 362 individuals (18+) 52.3%female 1 januari 1996 - 31 December 2013)	PM10 AND Cancer mortality (CAVE Trachea, bronchus and lung cancer not just lung cancer)	Not adjusted for smoking.
Weichenthal et al., 2017[21]	1.09 (1.06 - 1.12) 5-year lag	Land use regression model	1.1 million adults who resided in Toronto, Canada and who were followed for disease incidence from April 1, 2001 to December 31, 2012 and a 5-year lag in exposure was used	PM2.5 AND lung cancer incidence	Indirectly adjusted for smoking using a method created by Shin et al.[12]

Pinault et al., 2017[22]	1.128 (1.073 - 1.186)	A national model incorporating ground level data	2.4 million people aged 25–90 years followed for 10years.	PM2.5 AND Lung cancer mortality	Not adjusted for smoking
Weichenthal et al., 2016 [23]	1.050 (1.001 - 1.100)	Ground monitoring data	193,300 people living in a radius of 5km to a ground monitor from 1991 until 2009	PM2.5 AND Lung cancer mortality	Indirectly adjusted for smoking using a method created by Shin et al.[12]
Hart et al., 2015[24]	1.17 (0.93, 1.47)	Land-use regression model	cohort of 4,666 members September 1986-31 December 2003,	PM2.5 AND lung cancer incidence	Adjusted for smoking
Puet et al., 2014 [25]	1.04 (0.95 - 1.14)	Ambient GIS-based spatiotemporal exposure model predictions based on ground monitoring.	121,700 female participants from 1994 through 2010	PM10 AND lung cancer incidence	Adjusted for smoking
Puet et al., 2014 [25]	1.06 (0.91 - 1.25)	Ambient GIS-based spatiotemporal exposure model predictions based on ground monitoring. Before 1999 PM 2.5 was modeled using data on PM10	121,700 female participants from 1994 through 2010	PM2.5 AND lung cancer incidence	Adjusted for smoking
Carey et al., 2013[26]	1.12 (1.05–1.20)	The pollutant concentrations were estimated using air dispersion models based on ground monitoring	835,607 patients aged 40–89 years followed from 2003–2007	PM10 AND lung cancer mortality	Adjusted for smoking
Carey et al., 2013[26]	1.14 (1.07–1.22)	The pollutant concentrations were estimated using air dispersion models based on ground monitoring	835,607 patients aged 40–89 years followed from 2003–2007	PM2.5 AND lung cancer mortality	Adjusted for smoking
Cesaroni et al., 2013[27]	1.02 (0.98 - 1.07)	Flexible air quality regional model (a	1,265,058 residents	PM2.5 AND	Not adjusted for smoking

		Eulerian dispersion model) using ground monitoring	21 October 2001-December 2010	lung cancer incidence	
Heinrich et al., 2013[28]	1.84 (1.23 - 2.74)	Nearest air-monitoring station data	4800 women aged 55 years from North Rhine-Westphalia, Germany, were followed for up to 18 years	PM10 AND lung cancer mortality	Adjusted for smoking
Hales et al., 2012[29]	Odds ratio 1.015 (1.004 - 1.026)	Were estimated based upon athmospheric modelling for one city extrapolated using multiple predictors	1.06 million adults for 3years.	PM10 AND lung cancer mortality	Adjusted for smoking
Turner et al., 2011[30]	1.15 (0.99 – 1.35)	Multiple methods were used, unclear how they averaged all these methods together.	375,083 lifelong never-smokers were retained for the present analysis 26 year follow up.	PM2.5 AND lung cancer mortality	Adjusted for smoking
Beelen et al., 2008[31]	1.06 (0.82 – 1.38)	Estimated regional background concentrations using inverse distance weighed interpolation of concentrations measured at regional background sites in the National Air Quality Monitoring Network (NAQMN)	120,852 subjects (58,279 men and 62,573 women) aged 55-69 years were followed from 1 January 1987 to 31 December 1996.	PM10 AND Lung cancer mortality	Adjusted for smoking
Tomczak et al., 2016[32]	1.40 (1.16–1.69)	GEOS-Chem chemical transport model, as represented by the ratio of mean pm2.5 simulated during successful satellite	89,234 women with a start of follow up between 1980 and 1985 until 2004.	PM2.5 AND Lung cancer incidence	Adjusted for smoking

		retrievals, and pm2.5 simulated during the entire time period			
Villeneuve et al., 2015[33]	0.97 (0.80, 1.18)	GEOS-Chem chemical transport model, as represented by the ratio of mean pm2.5 simulated during successful satellite retrievals, and pm2.5 simulated during the entire time period	89,234 women with a start of follow up between 1980 and 1985 until 2004.	PM2.5 AND Lung cancer mortality	Adjusted for smoking
Beeson WL et al., 1998 [34]	RR = 1.13 (0.64-2.02)	From 1987 using ground monitoring data, the method used before is unclear	6,338 non-smoking, nonHispanic, white adult residents Followed from 1976 to 1992	PM10 and lung cancer incidence	Adjusted for smoking history
Fischer P. et al. 2015[35]	1.16 (1.11 – 1.20)	LUR model	7 million adults ≥ 30 years of age followed from 1 January 2004 to 1 January 2011.	PM10 and lung cancer mortality	Adjusted for smoking

Table 1 Results

Study	Hazard ratio(95% CI)	Measurement method PM	Population	Subject researched	Adjustments HR
Nilsson Sommar et al., 2021[36]	0.89 (0.49 - 1.59) Lags 6-10 years before the event	A dispersion model using detailed emission inventories	68 679 individuals Several ways of follow up	PM10 AND lung cancer mortality	Adjusted for smoking,…
Nilsson Sommar et al., 2021[36]	1.12 (0.65 - 1.93) Lags 1-5 years before the event	A dispersion model using detailed emission inventories	68 679 individuals Several ways of follow up	PM10 AND lung cancer mortality	Adjusted for smoking,…

Nilsson Sommar et al., 2021[36]	1.12 (0.61 - 2.04) Lags 1-5 years before the event	A dispersion model using detailed emission inventories	68 679 individuals Several ways of follow up	PM2.5 AND lung cancer mortality	Adjusted for smoking,…
Nilsson Sommar et al., 2021[36]	0.90 (0.45 - 1.82) Lags 6-10years before the event	A dispersion model using detailed emission inventories	68 679 individuals Several ways of follow up	PM2.5 AND lung cancer mortality	Adjusted for smoking,…

Table 2 Results Multi cohort study

This multi cohort study[36] might seem an ugly duckling in our other studies but has similarities for example with the ELAPSE study[13]. Even certain Cohorts like the SDPP[37] (Stockholm Diabetes Prevention Program) were also included in the ELAPSE study. I would not call this study a meta-analysis given that the data is calculated in a similar way using multiple cohorts but our concluding numbers are an analysis of all four cohort studies studied separately and then meta analysed for one conclusion. As noted by peer reviews this meta-analysis was not necessary per se and they could have pooled these results.
What is interesting about this study is that the time of exposure is lagging in time.
The conclusion is a combined analysis using the calculated HR's of all four cohorts.
The results lagging 1-5 years for both PM 2.5 and PM 10 associating with lung cancer mortality are positive but non-significant. The results lagging 6-10years are non-positive and non-significant for both PM 2.5 and PM10.
Both the way of calculating the results and the lag time make this study an ugly duckling in our other reported cohort studies. But not irrelevant.

Discussion:

In these 23 cohort studies there were 30 analysis performed examining PM and lung cancer. There was a significant positive correlation between PM and lung cancer mortality/incidence in 14 out of the 30 analysis.
Four analysis show a negative (non-significant) correlation, while all the remaining show a positive non-significant correlation.
This trend towards a positive correlation between PM and lung cancer is consistent with previous research.[3,38–41]

Interesting to note is that in Nilsson Sommar et al., 2021[36] the correlation between PM and lung cancer mortality was positive when the lag time was 1-5 years but negative when lag time was 6-10years.
Note that the concentrations of PM were relatively low, lower than European Union standards.

Multiple data points were extracted from the cohort studies. A clear trend towards a positive correlation was found but note that there are limitations to our study.
Our search strategy was optimised to the best of our ability.

To interpret our results correctly we will discuss the limits of our studies by talking about
- The measurement methods used to estimate PM exposure
- The timing of the studies
- The confounding factors
- Indoor pollution
- Causality
- PM as a collective noun

Measurement method PM

Modelling appears to be the main approach for estimating PM exposure. But Nabizadeh et al [42] found that studies using fixed monitoring stations had more significant results than those using only modelling methods.[42] In Bauwelinck, M et al.[10] a clear difference is seen in the hazard ratio when the measurement method of PM is changed. This is because these methods are no perfect representation of the exposure to PM.

RIO-IFDM and Hybrid LUR are both based on air pollution monitoring data, satellite air pollution data and take into account traffic line sources. The differences are that RIO-IFDM also takes into account meteorological data and the estimates apply to a much smaller area.[10]
Recommended strategies to better estimate PM exposure are for example the usage of GPS tracking of individuals and geographic information systems (GIS) .[42]

Would the measured exposure to PM be much greater if PM was measured in real time or if GPS tracking was used in combination with estimates per location adjusted for time exposure? Better quality studies could focus on this to further examine the significance of PM exposure.

Timing

Timing of the studies could influence the results because advances in medical science decrease the mortality rate of lung cancer.[43] This weakens the positive association between air pollution and lung cancer mortality that has been observed in more recent studies.

Confounding factors

Adjustment for smoking was noted for every study. This seemed important since smoking is an important risk factor for lung cancer.
Previous research also notes that considering confounding factors is important in observational studies.[44]
It can be said that most studies adjusted for smoking. Only 5 analysis did not account for smoking in any way. Of these all found a positive correlation between PM and lung cancer. Only two were significant.
This limitation was addressed in Cesaroni et al.[27] and they concluded that smoking would be an unlikely confounder since there was no association between PM 2.5 exposure and smoking. They also performed a statistical analysis of air pollution exposure and non-accidental mortality showing no difference when correcting for smoking.[27]
With all the information above in mind, and given that most studies are adjusted for smoking, smoking does not seem to influence the observed trend towards a positive correlation between PM and lung cancer.

Indoor pollution

All the studies above do not take into account indoor pollution
Asikainen A et al[45] state: “An annual loss of 2.1 million Disability-adjusted life years (DALYs) in EU-26 is associated to indoor and outdoor originating pollutants with more than half of it (1.28 million DALYs) caused by exposures to outdoor air pollution indoors and the remaining 0.74 million DALYs caused by indoor source pollutants.”[45]
The estimates of PM in the described cohorts do not take into account indoor PM.
This is a serious limitation to our study, since we want to know the relationship between PM and lung cancer and not the relationship between outdoor PM and lung cancer.
Solutions for indoor pollution:
There are models that estimate that by optimising ventilation rates; filtration of outdoor air; and; indoor source control we can reduce health risks, varying from 20 % to 44 %.[45]
Candles could be an example of an avoidable exposure to PM[46].

Causality

Causality cannot be proven in these cohort studies. Therefore we looked at other studies and expert opinions. There seems to be a limited understanding about which components of PM2.5 are responsible for increasing the risk of lung cancer.[13]

Animal studies have shown that exposure to PM2.5 causes pathological damage and affects levels of inflammatory cytokines and oxidative stress factors in the lungs of rats.[47]
An in vitro study shows that PM inhibits DNA repair by inhibiting nucleotide excision repair(NER).[48]
Jingonli et al.[49] reviewed the current knowledge about epigenetic changes and PM exposure and it suggests that PM induces epigenetic changes in all three classes: DNA methylation, histone modification and miRNA. They conclude that these epigentic changes may be partially responsible for the rise in lung cancer incidence.
It should not be overlooked that PM contains metals and polycyclic aromatic hydrocarbons (PAHs), which are known carcinogens themselves. [49]
The metals found in PM are reported to be a possible catalyst for PM-related airway inflammation and injury through the Fenton reaction.[46]
In one of the international agency for research on cancer (IARC) monographs they state the following: “The international agency for research on cancer (IARC) Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as carcinogenic to humans (IARC Group 1), based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence.”[50]
They also state that PM2.5 is increasingly used as an indicator pollutant.[50]

Given the forementioned studies and expert opinion on the matter causality seems to be likely. And is to be further examined in future studies.

PM is a collective noun

Zheng et al.[51] found a different composition of PM2.5 in different seasons and different areas across the southeastern US. In this study the major contributions to PM2.5 mass concentrations were secondary sulfate (30 (±6%)), wood combustion (15 (±12%)), diesel exhaust (16 (±7%)), secondary ammonium (8 (±2%), secondary nitrate (4 (±3%)), meat cooking (3 (±2%)), gasoline-powered motor vehicle exhaust (2 (±2%)), and road dust (2 (±2%)).
In conclusion, depending on the location of where you are, your exposure to PM even though at the same concentration might lead to different health risks depending on the composition.
An interesting conclusion of Hvidtfeldt et al. was that their results found an increased risk of lung cancer associated with sources of combustion particulate matter rather than with non-exhaust traffic emissions.[13]

Strengths of our study:
A large number of studies were included. The systematic approach itself should be noted as a strength.
Only cohort studies were included, these had large numbers of participants. Our sample population was western which makes it representable and relevant for the Belgian population.

Future perspectives:
Air quality seems to remain important even when already suffering from lung cancer, in a previous cohort study, lung cancer survival correlated positively with air quality.[52]
This gives a new perspective, indicating that air quality is a possible co-treatment option.
Should we examine people’s living situations, proximity to busy roads? Should we actively recommend indoor ventilation, especially in those at risk?
Further research is needed.

Conclusion:
Pubmed and embase were systematically searched for cohort studies concerning lung cancer and PM. 23 cohort studies met all our inclusion criteria. They performed 30 analysis of which all, except 4 pointed to a positive correlation between PM and Lung cancer

mortality/incidence. This is consistent with previous research, but now in a Western population, and therefore our results are representative and relevant to the Belgian population.

Declaration of Competing Interest

None.

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