EDITOR'S CHOICE

Biomarkers of ambient air pollution and lung cancer: a systematic review

Christiana A Demetriou,[1,2] Ole Raaschou-Nielsen,[3] Steffen Loft,[4] Peter Møller,[4] Roel Vermeulen,[5] Domenico Palli,[6] Marc Chadeau-Hyam,[1] Wei W Xun,[1] Paolo Vineis[1]

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[1]Department of Epidemiology and Biostatistics, Imperial College London, London, UK
[2]Department of Electron Microscopy and Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus
[3]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark
[4]Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[5]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
[6]Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute—ISPO, Florence, Italy

Correspondence to
Christiana A Demetriou
Department of Electron Microscopy and Molecular Pathology The Cyprus Institute of Neurology and Genetics PO Box. 23462, 1683 Nicosia Cyprus; christiana.demetriou08@imperial.ac.uk

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ABSTRACT

The association between ambient air pollution exposure and lung cancer risk has been investigated in prospective studies and the results are generally consistent, indicating that long-term exposure to air pollution may cause lung cancer. Despite the prospective nature and consistent findings of these studies, causality assessment can benefit from biomarker research. In the present systematic review, we assess the contribution of intermediate biomarkers in epidemiological studies, to ascertain whether their measurement reinforces causal reasoning. We have reviewed 524 papers which described the relationships between ambient air pollution and biological markers of dose and early response. The evidence for each marker was evaluated using assessment criteria which rate a group of studies from A (strong) to C (weak) on amount of evidence, replication of findings, and protection from bias. Biomarkers that scored A or B for all three criteria are included here. The markers that fulfilled the inclusion criteria are: 1-hydroxypyrene, DNA adducts, chromosomal aberrations, micronuclei, oxidative damage to nucleobases, and methylation changes. These biomarkers cover the whole spectrum of disease onset and progression from external exposure to tumour formation and some have also been suggested as risk predictors of future cancer, reinforcing causal reasoning. However, methodological issues such as confounding, publication bias and use of surrogate tissues instead of target tissues in studies on these markers are of concern. The identified biological markers have potential to shed light on the pathways of carcinogenesis, thus defining the association more clearly for public health interventions.

AIR POLLUTION AND LUNG CANCER: STRENGTH OF EVIDENCE

The association between exposure to ambient air pollution and the risk of lung cancer has been evaluated in a number of prospective studies, which are summarised in supplementary online table 1. The evidence linking exposure to urban air pollutants, mainly particulate matter ($PM_{2.5}$ or PM_{10}), with lung cancer is generally consistent, albeit formal statistical significance was not always reached. Cohorts from the USA as well as from Europe demonstrated increased risks of lung cancer with higher exposure to PM and other substances present in polluted air, with statistically significant risk ratios ranging from 1.14 to 5.21 (see supplementary online table 1 for references).

The main strength of the studies above resides in their prospective nature, with exposure being assessed long before disease ascertainment. However, causality is still uncertain, as a recent document by the Health Effects Institute has stressed.[1] In the present systematic review we evaluate the contribution of biological markers of internal dose, biologically effective dose, and early effect in epidemiological studies on air pollution, to ascertain whether such contribution reinforces causal reasoning.

Measurement of biological markers of dose and effect can improve investigation of the health effects of various exposures, including air pollution, by facilitating improved exposure assessment and increased understanding of mechanisms, thereby providing biological plausibility, and investigation of individual susceptibility.[2]

This review aims to identify biological markers of dose and effect for which there is consistent evidence in the literature, to support the results of epidemiological studies on the effects of ambient air pollution. Epidemiological evidence from the selected studies has been assessed using a set of criteria that have been developed elsewhere.[3] These account for (1) the total number of subjects investigated, (2) the degree of replication of findings across studies, and (3) potential protection from bias and/or confounding. PRISMA guidelines were also used to structure the analyses and to report the results.[4]

METHODS

Search strategy and selection criteria

Online databases PUBMED and OvidSP were searched to identify papers that evaluated the effects of ambient air pollution using biological markers up to January 2012. This search encompassed studies on subjects who have been exposed to environmental air pollution at their place of residence or at work, including traffic related air pollution. As illustrated in online supplementary figure 1,[5] search terms included 'ambient' and 'traffic-related air pollution', 'particulate matter', 'polycyclic aromatic hydrocarbons', 'benzene', 'NO_x', and 'SO_x'. References within each paper found during the initial search were also investigated and relevant papers identified. The resulting papers evaluated exposure using a variety of methods: personal air sampling, ambient pollution data from monitoring sites close to the place of residence or workplace, or traffic density in the place of residence. Only papers published in English were reviewed. The final reference list was based on relevance to the broad scope of this review, with papers without relevant exposure or outcome,

studies on animals or in vitro studies, and perspectives and opinion reviews all excluded.

Papers were categorised according to the type of biological marker under investigation. As illustrated in figure 1,[6] biomarkers can reflect each step in a causal pathway from exposure to disease. They are usually grouped as biomarkers of: (1) internal dose; (2) biologically effective dose, indicating how much the exposure has damaged the molecules in the body and has possibly been removed by metabolic or repair mechanisms; (3) biological effects indicating changes in function or permanent alterations; (4) disease; and (5) susceptibility, which can modify transition rates at each step. Based on the figure, the biomarkers in this review were defined as biological markers of: (1) internal dose, which included 1-hydroxypyrene (1-OHP); (2) effective dose, which included DNA adducts and oxidised nucleobases; and (3) early effect, which included chromosomal aberrations (CAs), sister chromatid exchanges (SCEs) and micronuclei (MN), as well as mutations in the *Hypoxanthine phosphoribosyltransferase* (HPRT) gene and changes in methylation patterns. As explained in the Discussion section, we have not examined markers of genetic susceptibility related to gene variants or markers of inflammation. Figure 1 also shows the location of each of these biological markers in the pathway to disease. The response and step transition time can vary at each step with half-lives of, for example, 1-OHP, oxidised nucleobases and gene expression counted in hours, whereas bulky adducts show half-lives of weeks and for CAs and MN the half-life can be years. In lung cancer pathogenesis, the central mechanisms are considered damage to DNA in the form of bulky adducts and base oxidation from biotransformed polycyclic aromatic hydrocarbons (PAHs) and oxidative stress, as well as inflammation, with resulting chromosome damage and mutations. These changes, together with altered gene regulation, can lead to loss of cell cycle control and genomic instability.[2]

Evaluation criteria

For each biological measure, epidemiological evidence from the corresponding papers was assessed by generalising the Venice criteria, which were initially developed in the context of genetic association studies.[3] These criteria are based on a scoring strategy according to three characteristics: (1) amount of evidence (sample size); (2) results replication; and (3) protection from potential bias and/or confounding. As detailed in table 1, biological markers of dose and effect with a large amount of evidence (total sample size >1000) were scored with A for amount of evidence.[3] Similarly, markers extensively replicated among studies scored A for replication, provided that at least one well conducted meta-analysis with limited between-study heterogeneity was available. However, meta-analyses being rare in this field, some markers were scored A only on the basis of clear result replication (ie, unambiguous agreement in showing or not showing a significant association). Biological markers were finally scored A for protection from bias if potential bias could affect the magnitude but not the presence of the association, with B if there was no obvious bias that could affect the presence of the association but there was considerable missing information concerning possible bias, and with C if the studies demonstrated potential for bias that could affect the presence or absence of the association. Confounding and publication bias are two important limitations of the studies we assessed, to which we have devoted a specific section in this review. In particular, we have assessed publication bias separately at the end of the Results section. The analytical methodology as well as reporting were based on the PRISMA guidelines.

It is recognised that the studies are heterogeneous within the specific exposure circumstances that they evaluate, and this may contrast with the application of a single score for the assessment of causality. However, the general exposure studied in this review is ambient air pollution and all the reviewed studies can be grouped under this broad category.

In the present review, only biological markers of internal dose, biologically effective dose and early effect that scored A or B for all three criteria are included: 1-OHP, DNA adducts, CAs, MN, oxidised nucleobases and methylation changes. SCEs and HPRT mutations were not considered further as they failed to score A or B for the three criteria. Data from relevant studies were extracted and are summarised in online supplementary tables 1–10. Quantitative meta-analyses were not performed, owing to the large heterogeneity between the included studies. However, for clarity, the results for DNA adducts, oxidised nucleobases and CAs were summarised as standard mean differences (SMD) in forest plots.

We have focused on genotoxic and epigenotoxic effects as markers of biologically effective dose and biological effect directly related to carcinogenesis. Although chronic inflammation is considered relevant to particle-induced lung carcinogenesis,[7] at least one mechanism of action is thought to involve oxidative stress-induced DNA damage, which is addressed here.[8] While exposure to air pollutants has been associated with acute inflammation in the airways and to elevated levels of systemic markers of inflammation, such as C reactive protein and

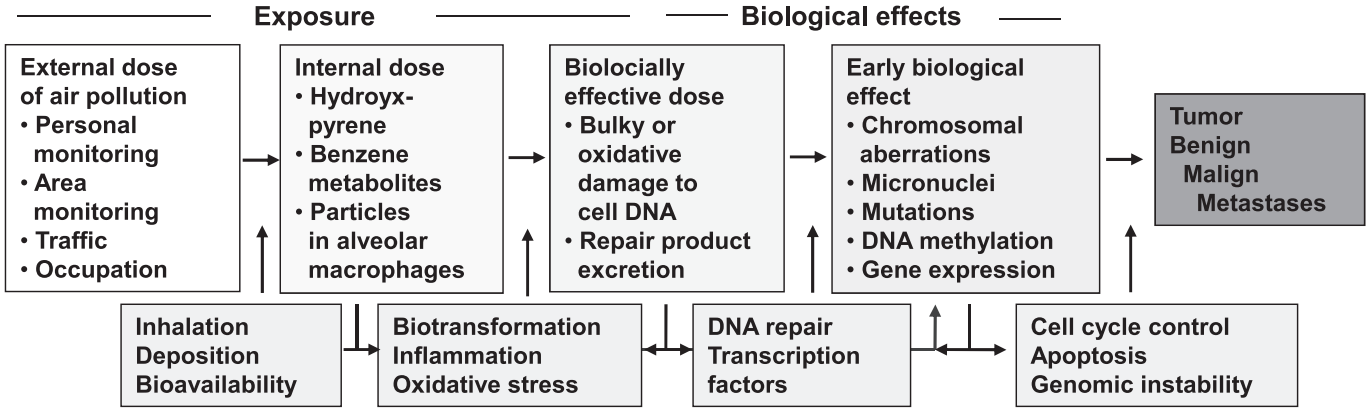

Figure 1 Biological markers of exposure and effects of air pollution. Adapted from Loft *et al*.[5]

Table 1 The grading criteria for the evaluation of cumulative evidence on the relationship between air pollution and biomarkers

Criteria	Categories	Proposed operationalisation
Amount of evidence	A: Large-scale evidence B: Moderate amount of evidence C: Little evidence	Thresholds may be defined based on sample size, power or false-discovery rate considerations. As a simple rule, we suggest that category A requires a sample size of over 1000 (total number in cases and controls assuming 1:1 ratio) evaluated in the least common genetic group of interest; B corresponds to a sample size of 100–1000 evaluated in this group, and C corresponds to a sample size of <100 evaluated in this group.
Replication	A: Extensive replication including at least one well-conducted meta-analysis with little between-study inconsistency B: Well-conducted meta-analysis with some methodological limitations or moderate between-study inconsistency C: No association; no independent replication; failed replication; scattered studies; flawed meta-analysis or large inconsistency	Between-study inconsistency entails statistical considerations (eg, defined by metrics such as I^2, where values of 50% and above are considered large, and values of 25%–50% are considered moderate inconsistency) and also epidemiological considerations for the similarity/standardisation or at least harmonisation of phenotyping, genotyping and analytical models across studies.
Protection from bias	A: Bias, if at all present, could affect the magnitude but probably not the presence of the association B: No obvious bias that may affect the presence of the association, but there is considerable missing information on the generation of evidence C: Considerable potential for or demonstrable bias that can affect even the presence or absence of the association	A prerequisite for A is that the bias due to phenotype measurement, genotype measurement, confounding (population stratification) and selective reporting (for meta-analyses) can be appraised as not being high plus there is no other demonstrable bias in any other aspect of the design, analysis or accumulation of the evidence that could invalidate the presence of the proposed association. In category B, although no strong biases are visible, there is no such assurance that major sources of bias have been minimised or accounted for because information is missing on how phenotyping, genotyping and confounding have been handled. Given that occult bias can never be ruled out completely, note that even in category A, we use the qualifier 'probably'.

Adapted from Ioannidis *et al*. *Int J Epidemiol* 2008;**37**:120–32 (See supplementary file for references).

fibrinogen, this has so far mainly been associated with the risk of cardiovascular diseases.[9]

RESULTS

Biological markers of exposure and internal dose: 1-OHP

1-OHP is a useful marker for occupational exposure and has also become the biomarker most commonly used to assess exposure to traffic-related air pollution and particularly to PAHs. It is a urinary excreted metabolite of pyrene and can be measured as a marker of systemic absorption of PAHs.[10 11]

Based on our inclusion criteria, eight papers and one review studied the association between exposure to air pollution or chemicals in polluted air and the levels of 1-OHP excretion in the urine of exposed individuals. Online supplementary tables 2 and 3 summarise the associations reported in these studies. Some of the studies suggested positive associations in adults, for example, mail carriers and bus drivers,[12–14] and other studies showed higher 1-OHP levels in exposed children.[15–19]

Confounding

Among the studies on 1-OHP, five adequately adjusted for confounders including smoking data, where relevant.[13 15–17 19] One of the studies only adjusted for smoking,[14] one did not mention confounding[18] and one was a review.[12]

Grading

The 1-OHP information was graded A for evidence, A for replication and B for bias. Although the overall number of subjects is large (N=1708) and findings have been replicated several times, it is not completely clear whether confounding from smoking, occupational exposures or environmental tobacco smoke can be ruled out, which justifies a B for the third grading criterion.

Biological markers of exposure and effective dose: DNA adducts

DNA adducts are formed when carcinogens, or metabolites of carcinogens, react with sites in DNA, resulting in the formation of a covalent bond between the carcinogen and DNA. Even though adducts can be removed by repair proteins, some can persist. This can result in nucleotide substitutions, deletions and chromosome rearrangements during replication, contributing to cancer development.[20] Numerous studies have considered DNA adducts as a biomarker of exposure to genotoxic carcinogens. The studies reported here (N=25) are cross-sectional and case–control studies, some of which were nested in prospective cohorts. Some studies carried out correlation and regression analyses on all subjects (online supplementary table 4), while others compared the mean DNA adduct levels in individuals with estimated high or low external exposures (online supplementary table 5). As illustrated in figure 2, most studies (including two reviews) suggested positive associations between exposure to air pollution or chemicals in polluted air and the formation of DNA adducts in exposed individuals. Subjects in these studies included, among others, policemen in Bangkok,[14] schoolchildren in Thailand,[17] policemen in Genoa[21] and in Prague,[22] residents in an industrial area and rural controls in Poland,[23] bus and taxi drivers in Stockholm,[24] bus drivers in Copenhagen,[25] students in Denmark and in Greece,[26] as well as street vendors, taxi drivers, gasoline salesmen and roadside residents in Benin.[27] Fetal exposures and DNA adducts in newborns also showed positive associations.[28–30] Only two studies reported no association.[31 32]

Confounding

Of 14 studies investigating DNA adducts which adjusted for a number of confounders, seven adjusted for PAHs in diet. One study adjusted only for smoking, and one only for various risk alleles. For six studies there is no information on confounding. Two publications were reviews and for one study confounding was not mentioned by the authors as the measurements were from the same subjects before and after a change in working conditions, within a 3-month interval, during which exposure to potential confounder(s) can be assumed to be constant (online supplementary table 6a).

Grading

The DNA adducts information was graded A for evidence, A replication and B for bias. The association between ambient air pollution and DNA adducts has been shown in a large number of subjects (N=3075) and replicated. Confounding is unlikely in the studies that included only never and ex-smokers such as

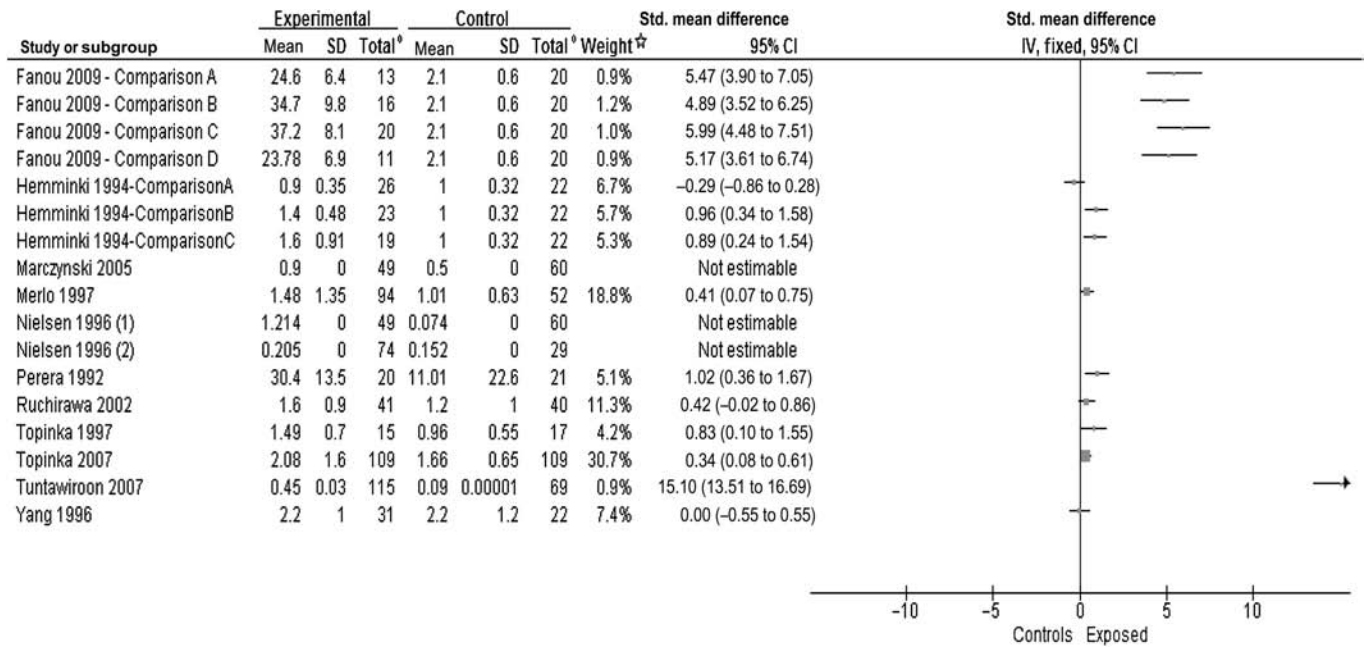

Figure 2 Standardized mean difference forest plot of studies on DNA adducts reporting difference in means. Weight was derived using the inverse of the variance in a fixed effects model. Forest plots are presented for clarity in data presentation. However, formal meta-analysis was not performed due to the heterogeneity of the studies included in the review. Total refers to total sample size in the experimental (exposed) and control groups (See supplementary file for references).

Peluso *et al*.[33] However, publication bias cannot be entirely excluded (see Publication bias and heterogeneity section below) and a major determinant of DNA adducts is diet[34] (which was not ascertained in most studies), so we rate B for the third grading criterion. It is important to mention that the levels of DNA adducts in white blood cells (WBCs) have been shown to predict the risk of lung cancer in cohort studies and recently in a prospective pooled analysis.[35]

Biological markers of exposure and effective dose: oxidised nucleobases

More data are available (N=34 publications) concerning oxidised nucleobases to nucleobases as this is one of the most plausible mechanisms by which air pollutants may affect lung pathophysiology (online supplementary figure 2). Oxidised nucleobases refers to modified purine and pyrimidine bases formed when reactive oxygen species (ROS) react with DNA or the nucleotide pool. Substances such as PM can generate ROS directly or through enzymatic reactions in target or inflammatory cells[36]; ozone and NO_2 are themselves reactive species, and benzene metabolism can also generate ROS.[10] Oxidatively modified DNA bases have the potential to damage the integrity of the genome. For example, 8-oxo-7,8-dihydroguanine (8-oxoGua), one of the most critical lesions, leads to GC to TA transversion unless repaired prior to DNA replication. Cell levels of 8-oxoGua are usually measured as its 2′-deoxyribonucleoside equivalent 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG). The most relevant repair in terms of base excision results in 8-oxoGua, which, however, is difficult to measure in urine, whereas 8-oxodG resulting from other putative repair pathways and nucleotide pool sanitisation can be readily calculated. Lastly, formamidopyrimidine DNA glycosylase (FPG) sensitive sites in mononuclear blood cells (MNBC) are a marker of oxidative damage. FPG is a base excision repair enzyme which recognises and removes oxidised purines, including 8-oxoGua.

The effects of air pollution on oxidised nucleobases have been studied in controlled exposure scenarios, in panel and in cross-sectional studies (online supplementary tables 6 and 7). The results of studies comparing mean levels of markers of guanine oxidation (8-oxodG or 8-oxoGua) are summarised in a forest plot (figure 3) which illustrates that for the majority of studies, biomarker levels are higher in exposed subjects compared to controls (positive SMD).

The effect of controlled exposure to air pollution (mainly traffic generated ultrafine particles with diameter <100 nm) has been investigated in healthy humans showing usually a higher level of FPG sensitive sites in MNBC in the exposed subjects than in the unexposed.[37–39] In addition, increased urinary excretion of 8-oxoGua was observed in studies where subjects were exposed to exhaust in traffic-intense areas.[40 41]

A number of panel studies which have also investigated the effects of air pollution in the general population showed contradictory effects of air pollution on oxidised nucleobases.[31 42 43]

The cross-sectional studies investigating the effect of air pollution on oxidised nucleobases can be grouped into two main categories according to their design. A first group of studies investigated the effect of air pollution among subjects with different occupational exposures. We refer here only to investigations in which the occupational exposure was qualitatively similar to the exposure of the general population (eg, we excluded categories with special exposures such as gasoline workers). Using job titles as the basis for stratification of exposure, subjects characterised by having jobs with high exposure to traffic emissions showed increased levels of oxidised nucleobases. A second group of residential studies generally showed positive associations between living and/or working in highly polluted areas and oxidised nucleobases. Studies using benzene as a marker of urban air pollution exposure also showed associations with markers of oxidised nucleobases.[27 44–47]

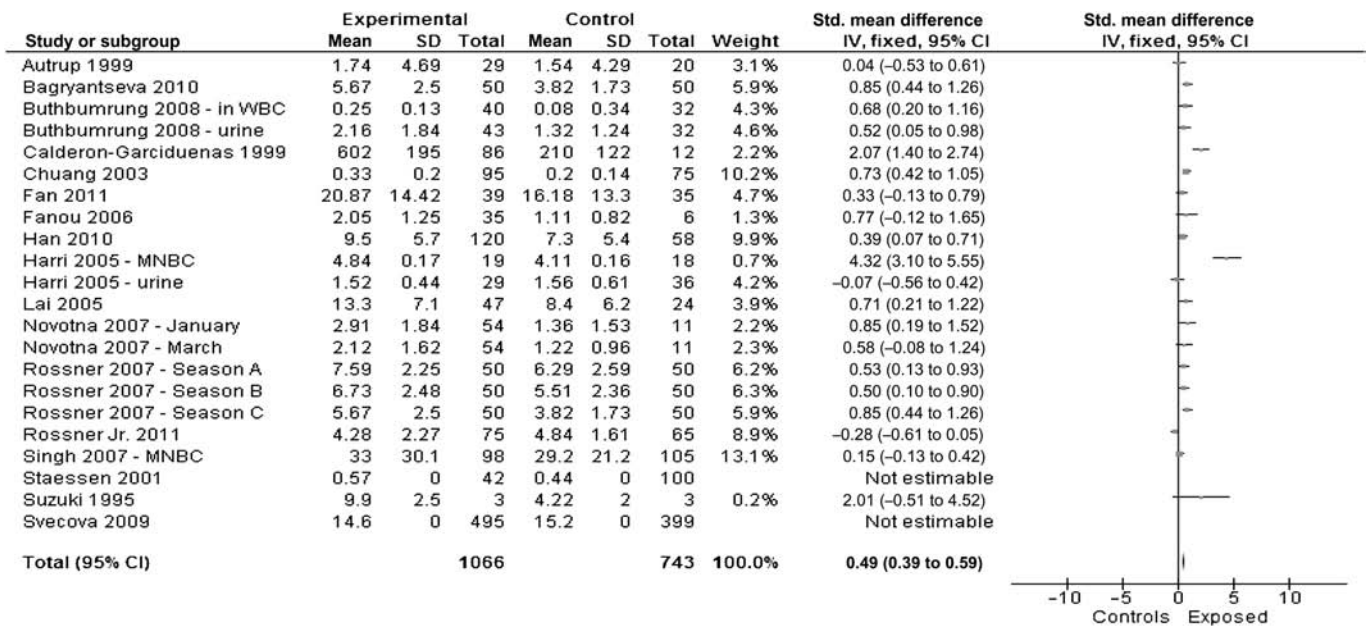

Figure 3 Standardised mean difference forest plot of studies on oxidised nucleobases reporting difference in means of 8-oxo-7,8-dihydro-2′-deoxyguanosine or 8-oxo-7,8-dihydroguanine. Weight was derived using the inverse of the variance in a fixed effects model. Forest plots are presented for clarity in data presentation. Total refers to total sample size in the experimental (exposed) and control groups (See supplementary file for references).

A formal meta-analysis of the effects of air pollution on DNA base oxidation (measured in MNBC) and excretion of repair products in urine, as well as an integrated analysis incorporating the endpoints of oxidatively damaged nucleobases in cultured cells, experimental animal models and humans, has been carried out.[48 49] Despite large heterogeneity between studies, the analysis showed highly significant effects with an SMD between exposed and unexposed subjects of 0.53 in blood (95% CI 0.29 to 0.76) and 0.52 in urine (0.22 to 0.82). Based on the studies included in the current review, we have replicated these findings (results not shown).

Confounding

Among publications on oxidised nucleobases (N=34), 23 adjusted for a number of confounders including smoking. Five studies adjusted only for metabolic genes and four studies were cross-over studies in short time frames, and confounding was therefore not relevant. For two studies there is no mention of confounders (online supplementary table 7a).

Grading

The oxidised nucleobases information was graded A for evidence, A for replication and A/B for bias. Altogether, there is consistent and strong evidence that exposure to ambient air pollution leads to increased levels of biomarkers of oxidation damage to nucleobases, both in observational and experimental studies. High urinary excretion of 8-oxodG or 8-oxoGua has been associated with increased risk of lung cancer in one prospective and several case–control studies.[6]

Biological markers of early effect: CAs

CAs are defined as modifications of the normal chromosome complement due to deletion, duplication or rearrangement of genetic material.

The studies on CAs (N=10) (online supplementary table 8) are not all supportive of a positive association with exposure to air pollution or its constituents in adults. As illustrated in figure 4, some studies found a higher frequency of CAs with exposure to heavy air pollution,[50–56] others did not find statistically significant associations[57 58] and others produced contradictory results.[59]

Confounding

Only six of the studies investigating CAs have adequately adjusted for confounders such as age, sex and smoking habits.[50–53 55 58] Three did not adequately adjust as they controlled only for age or only for sex.[54 56 59] One study did not mention adjustment for any confounders.[57]

Grading

The information on chromosome aberration was graded A for evidence, B for replication and B/C for bias. Even though not all studies agree, there is some evidence to support the association between exposure to air pollution and chromosome aberration frequencies. Confounding and publication bias cannot be ruled out.

Biological markers of early effect: MN

MN are nuclei, separate from and additional to the main nucleus of a cell. During cell division, DNA replicates and divides equally between the two daughter cells. If the process is disrupted, or the chromosomes are broken or damaged by chemicals or radiation, then the distribution of genetic material between the two daughter nuclei may be affected and pieces or entire chromosomes may fail to be included in either of the two daughter nuclei. The genetic material that is not incorporated into a new nucleus may form its own 'micronucleus'.[60] Thus, MN are a marker of chromosomal damage.

Four recent studies[21 56 61 62] and a review[63] have looked at the association between ambient air pollution or its constituents, and MN in the cells of exposed individuals (online supplementary table 9), finding positive associations.

Confounding

There is one review and four studies on MN, two of which have adjusted for smoking and gender,[61 62] and one included some

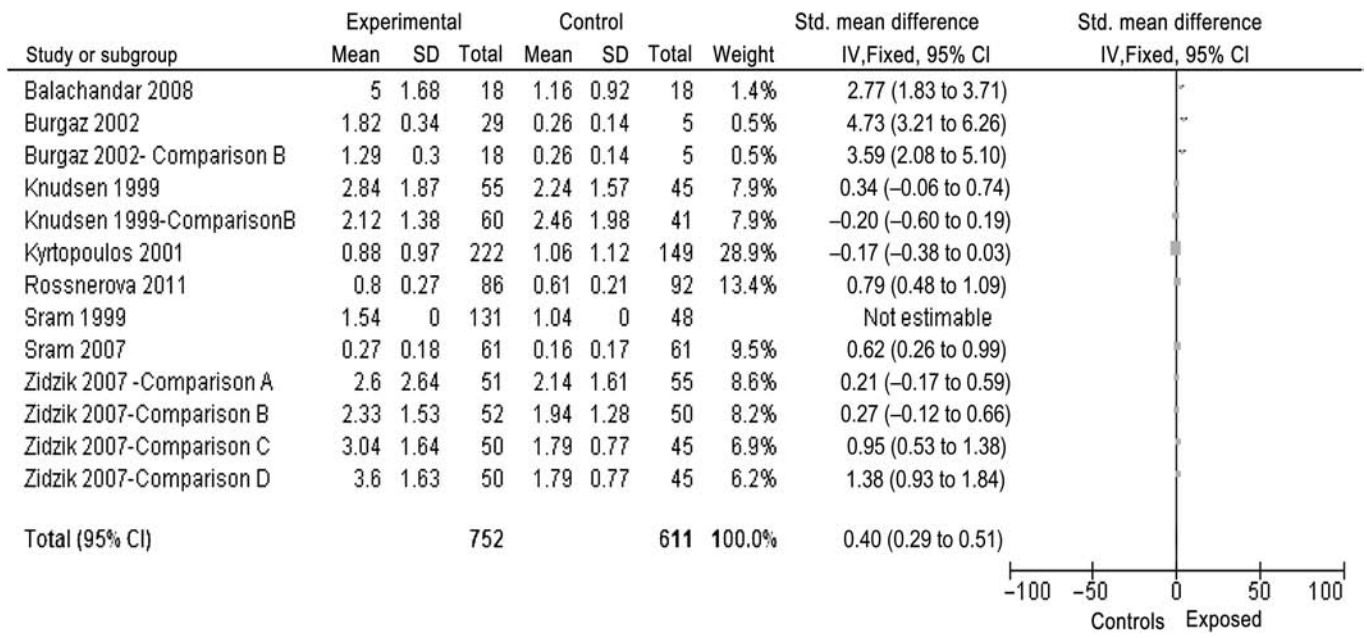

Figure 4 Meta-analyses: fixed effect model. Standardised mean difference forest plot of studies on chromosomal aberrations (CAs) reporting difference in means of CAs. Weight was derived using the inverse of the variance in a fixed effects model. Forest plots are presented for clarity in data presentation. However, formal meta-analysis was not performed due to the heterogeneity of the studies included in the review. Total refers to total sample size in the experimental (exposed) and control groups.

polymorphisms.[62] Two studies only adjusted for sex.[21 56] The study on newborns also adjusted for a number of relevant confounders.[61]

Grading

The information on MN was graded A for evidence, B for replication and B/C for bias. Given the replication of results between the studies, there is some evidence to support the association between exposure to air pollution and MN. However, confounding and publication bias cannot be entirely ruled out.

Biological markers of early effect: methylation patterns

DNA methylation refers to the addition of methyl groups to nucleotides. The genome has a well-established pattern of methylation. Increase or decrease of the methylated sites in DNA affects gene expression and can also lead to genomic instability. The degree of methylation is passed on to daughter strands at mitosis by maintenance DNA methylases. DNA methylation and the associated repressed or activated transcription of genes have been implicated in carcinogenesis.[64] Five reports (from four studies) have recently investigated the effects of air pollution exposure on methylation patterns,[30 65–68] mostly focusing on long interspersed element-1 (LINE-1) and Alu elements methylation as measures of whole genome methylation (online supplementary table 10). LINE-1 and Alu elements are retrotransposons, repetitive and mobile sequences in the genome. LINEs make up a large proportion of the genome and LINE-1 as well as Alu methylation correlates with overall level of DNA methylation in the cell. LINE-1 methylation was frequently found to be altered by exposure to air pollution,[65–68] and Alu methylation was also significantly altered in one study.[68] One study investigated global methylation in cord blood samples with the use of an assay kit and found that it was altered in response to prenatal PAH exposure.[30] These epigenetic changes can contribute to carcinogenesis at least as much as genetic changes.

Confounding

The five reports investigating methylation patterns have adequately adjusted for a number of clinical and environmental confounders, including smoking.

Grading

The information on methylation was graded as B for evidence, B/C for replication and B for bias. The results above suggest that LINE-1 methylation levels may be affected by exposure to air pollution or its constituents. Even though only a few studies were available, the replication between them was fairly good, thus supporting the B/C grading for replication. Alu methylation levels were less consistently affected. It is also relevant to note that LINE-1 methylation levels were found to increase with the level of exposure to some constituents of air pollution, for example PM_{10}, but to decrease with exposure levels to other constituents such as $PM_{2.5}$. Therefore, further evidence is needed to determine which constituents in air pollution affect methylation levels and in which direction, before we can more confidently draw conclusions about the effect of exposure to air pollution on methylation levels.

Publication bias and heterogeneity

One of the factors determining the third grading criterion is publication bias. As discussed, publication bias cannot be ruled out for most of the biological markers mentioned above. Funnel plots are a useful tool for checking the existence of publication bias, and a symmetric inverted funnel plot typically indicates that publication bias is unlikely. In this review, funnel plots could only be constructed for DNA adducts and oxidised nucleobases, where enough studies were available. Also, because of the diversity in effect estimates for each biological marker, only studies comparing mean levels of markers in cases and controls could be used. Moreover, different sample types (WBC, MNBC or urine), analytical methods and units were used for each marker. The funnel plots of SMDs (online supplementary

figures 3 and 4) were fitted using a fixed effects model and using the inverse variance as weight. The asymmetrical inverted funnels thus obtained demonstrate that publication bias may be a concern when the available evidence on biological markers of dose and effect and the relationship with air pollution is investigated. However, despite the asymmetry in the plots, the Egger's regression asymmetry test did not demonstrate a significant presence of publication bias for studies on DNA adducts or oxidised nucleobases (p=0.376 and p=0.576, respectively).

DISCUSSION

On the basis of the evidence from recent large cohort studies in the USA and in Europe (online supplementary table 1), it has been suggested that ambient air pollution may increase lung cancer risk.

Overall, existing biological markers of dose and effect appear to reinforce the causal nature of the association between air pollution and lung cancer, although the markers in this review are not all specific to lung carcinogenesis. DNA adducts, CAs, MN and oxidised nucleobase markers have been suggested to be predictive for the risk of future cancer.[35] The biological markers discussed in this review cover the whole spectrum of progression from external exposure to tumour formation (figure 1). 1-OHP is an excellent marker of internal dose, DNA adducts and oxidised nucleobases are markers of the biologically effective dose, while MN, CA and DNA methylation are good markers of early biological effect. The multilevel evidence supports a causal association between exposure to ambient air pollution and lung cancer. The available evidence is stronger for oxidised nucleobase markers, and the mechanisms supported by these biological markers are likely to be central to the biological process of air pollution induced lung cancer (figure 1).

However, certain aspects of biological markers used in epidemiological studies need to be clarified. These include their reliability, the extent to which markers interact with genetic susceptibility, and inter-laboratory as well as inter-technique variation. Adequate adjustment for confounding factors needs to be considered. In the studies summarised above, body mass index, physical exercise, consumption of charcoal-broiled food, consumption of fresh fruits and vegetables, and seasonal variations were rarely controlled for (online supplementary tables 2–10). All these factors have been reported to influence bulky DNA adducts. Most studies have controlled for smoking, one of the most relevant confounders regarding exposure to air pollution and biological markers. Finally, the association between air pollution and biological markers of dose and effect depends on the level of exposure, with low levels of exposure often leading to weak and non-significant associations.

An issue difficult to tackle in studies utilising biological markers, which are usually small in size, is publication bias. Funnel plots (online supplementary figures 3 and 4) do not show extensive publication bias. However, there is some asymmetry of the plots and there are only few large studies showing positive effects, implying some bias (online supplementary tables 2–10).

We have focused on genotoxic and epigenotoxic effects as markers of biologically effective dose and biological effect directly related to carcinogenesis, while we have not included markers of inflammation. Although chronic inflammation is probably relevant to particle-induced lung carcinogenesis, the overall evidence is still relatively scanty. Exposure to air pollutants has been associated with acute inflammation in the airways and to elevated levels of systemic markers of inflammation, such as C reactive protein and fibrinogen. A recent study found that medium-term exposure to traffic-related air pollution may induce an increased inflammatory/endothelial response, especially among people with diabetes.[69] So far the inflammatory response has mainly been associated with the risk of cardiovascular diseases rather than cancer.[9]

The main limitations we identified in our review are related to control of confounding and publication bias. In addition, almost none of the studies investigated more than one mechanistic pathway. Maybe the next generation of studies could address confounding in a more systematic way (eg, by measuring cotinine) and will include markers that refer to more than one pathway (eg, inflammation and epigenetics). Publication bias is a general problem in epidemiology and requires concerted action by journal editors.

Another important, and probably largely unavoidable, limitation of these studies is that they are based on surrogate tissues (eg, WBCs) that do not necessarily reflect changes in the target tissues. Due to the difficulties associated with obtaining lung tissue samples, surrogate tissues are used to estimate the damage caused in the target tissue. In the case of air pollution and lung cancer, lung tissue is the first point of contact with the carcinogen and therefore damage in this tissue is likely to be more pronounced than damage in surrogates such as WBCs.

In spite of methodological limitations, there is overall good evidence concerning the genotoxicity of air pollution. Applying grading criteria for causal assessment, we concluded that the cumulative evidence indicates that air pollution affects some of the biological markers related to carcinogenesis, particularly 1-OHP, DNA adducts and 8-oxodG and other oxidised nucleobases. Some markers of genotoxicity have also been found to be associated with lung cancer (DNA adducts and 8-oxodG/8-oxoGua in urine). Lung cancer develops via a series of progressive pathological changes in the respiratory epithelium. Molecular alterations such as loss of heterozygosity, gene mutations and gene promoter methylation have emerged as mechanisms of lung carcinogenesis.[2]

Although information obtained from biomarkers adds to the knowledge obtained from prospective epidemiological studies on the effects of air pollution, the evidence overall is still incomplete and fragmented. Not only is the evidence for several markers still equivocal, but we are far from being able to reconstruct the full pathogenetic pathway that leads from external exposure to the outcome of lung cancer. Few studies have been conducted on epigenetic and non-genotoxic changes, so that the evidence is skewed in favour of genotoxicity biomarkers. We propose that future efforts should be directed not only towards reducing uncertainty concerning the role of specific biomarkers, but also towards filling the gaps in the supposed pathogenetic pathways.

ADDITION TO SCIENTIFIC KNOWLEDGE AND CONCLUSIONS

Our review evaluated the data available on some of the most relevant biomarkers of air pollution exposure, and used well accepted criteria to grade the cumulative evidence on each biomarker with respect to the amount of evidence, replication and protection from bias. Several biological markers of dose and effect related to carcinogenic mechanisms, and especially oxidised nucleobases, have been found to be associated with exposure to ambient air pollution, and some of these markers have also been associated with risk for lung cancer.[35] These biological markers, which mark the continuum of progression from external exposure to cancer outcome, have the potential to shed light on the pathways of carcinogenesis, thus defining the association more clearly for public health interventions.

To our knowledge, this is the first time a systematic evaluation of the topic has been undertaken. Our review adds biological support to the relationship between air pollution and lung cancer. Nonetheless, future research to fill gaps in our knowledge of supposed pathogenetic pathways is needed.

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Contributors CAD wrote most sections of the manuscript, reviewed the whole document and is a guarantor; SL wrote the section on oxidative damage, contributed figures, and revised the manuscript critically for intellectual content; PM wrote the section on oxidative damage, contributed figures and revised the manuscript critically for intellectual content; OR-N, RV and MC-H presented ideas, provided critical comments on the conclusions and revised the manuscript critically for intellectual content; WX helped produce the funnel plots and revised the manuscript; PD revised the manuscript critically for intellectual content; and PV made a substantial contribution to the conception and design, and analysis and interpretation of data, revised the entire manuscript and is a guarantor.

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SUPPLEMENTARY MATERIAL

Title: Biomarkers of ambient air pollution and lung cancer: strength of evidence Christiana Demetriou[1,6], Ole Raaschou-Nielsen[2] Steffen Loft[3], Peter Møller[3], Roel Vermeulen[4], Domenico Palli[5], Marc Chadeau-Hyam[1], Wei W Xun[1], Paolo Vineis[1]

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Table 1 – Prospective study results on the relationship between exposure to air pollution and lung cancer incidence and/or mortality, listed by study or cohort

First Author, Year	Area/ Country	Exposure‡	Outcome	Controlled Confounders	Number of Subjects	RR†	CI†
AMERICAN STUDIES							
American Legion Study							
Buell, 1967	USA	>10 yrs in LAcounty vs.other counties	Lung Cancer Mortality	Age, sex, smoking, size of birthplace	336,571 person-yrs	2.5	*not reported
		>10yrs vs. <10yrs in LA county	Lung Cancer Mortality	Age, sex, smoking, size of birthplace		1.26	*not reported
ASHMOG Study							
Mills, 1991	USA	Total Suspended Particulate (exceedance frequency of 200µg/m3)	Cancer in females incidence	Age, sex, education, ex-smoking, ETS†, and occupational exposure	6,000	1.72	0.81-3.65
		Ozone (exceedance frequency of 10pphm)	Lung Cancer incidence	Age, sex, education, ex-smoking, ETS, and occupational exposure		2.25	0.96-5.31
Beeson, 1998	California, USA	Ozone (100ppb increase)	Lung Cancer incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use	6,338	3.56	1.35-9.42
		PM10† (IQR increase)	Lung Cancer Incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use		5.21	1.96-13.99
		SO_2 (IQR increases)	Lung Cancer Incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use		2.66	1.62-4.39
		PM10 exceedance frequencies of 50 microg/m3 (IQR increase)	Lung Cancer Incidence - females	Smoking, Age		1.21	0.55-2.66
		PM10 exceedance frequencies of 60 microg/m3 (IQR increase)	Lung Cancer Incidence - females	Smoking, Age		1.25	0.57-2.71
		SO_2 (IQR increases)	Lung Cancer Incidence - females	Smoking, Age		2.14	1.36-3.37
Abbey, 1999	USA	PM10 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use	6,338	3.36	1.57-7.19
		PM10 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		1.33	0.60-1.96

		Ozone (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		2.10	0.99-4.44
		Ozone (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		0.77	0.37-1.61
		SO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		1.99	1.24-3.20
		SO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		3.01	1.88-4.84
		NO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		1.82	0.93-3.57
		NO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		2.81	1.15-6.89
McDonnell, 2000	USA	PM2.5† (IQR increase = 24.3 μg/m3),	Lung Cancer Mortality		6,338	2.23	0.56-8.94
		PM2.5-10 (IQR increase = 9.7 μg/m3)	Lung Cancer Mortality			1.25	0.63-2.49
		PM10 (IQR increase = 29.5μg/m3)	Lung Cancer Mortality			1.84	0.59-5.67
American Cancer Prevention Study II							
Pope, 2002	USA	NO_2 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, smoking, education, marital status, body mass, alcohol comsumption, occupation, and diet	409-493 thousand	1.14	1.04-1.23
Jerrett, 2005	USA	PM10 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables	22,905	1.2	0.79-1.82
		Ozone (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables		0.99	0.91-1.07
		Distance to freeways (<500m vs. >500m)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables		1.44	0.94-2.21
Turner, 2011	USA	PM2.5 (10 microg/m3 increase) ACP	Lung Cancer Mortality	Age, sex, smoking, educational attainment, BMI, chronic lung disease	188,699	NA	1.15-1.27
Pope, 2011	USA	PM2.5 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, education, marital status, body mass, alcohol consumption, occupational exposures, smoking duration, and diet	1.2million	1.14	1.04-1.23
Harvard Six Cities Study							
Dockery, 1993	USA	Inhalable particles:	Lung Cancer	Age, sex, smoking, education, and BMI		1.27	1.08-1.48

		Most polluted vs. Least polluted city	mortality				
					8,111		
		Fine particles: Most polluted vs. Least polluted city	Lung Cancer mortality	Age, sex, smoking, education, and BMI		1.26	1.08-1.47
		Sulphate particles: Most polluted vs. Least polluted city	Lung Cancer mortality	Age, sex, smoking, education, and BMI		1.26	1.08-1.47
Krewski, 2005	USA	PM2.5 (most vs. least polluted city = 18.6 microg/m3 increase)	Lung Cancer Mortality	Age, sex, smoking, education, BMI, diabetes, occupational exposure to dust, gases or fumes	8,111	1.43	0.85-2.41
Laden, 2006	USA	PM2.5	Lung Cancer mortality	Age, sex, smoking, education, and BMI	8,096	1.27	0.96-1.69
			EUROPEAN STUDIES				
Cohort of Oslo men							
Nafstad, 2003	Norway	NO(x) (per 10 μg/m3 - home address)	Lung Cancer incidence	Age, smoking habits, and length of education	16,209	1.08	1.02-1.15
		SO_2 (per 10 μg/m3)	Lung Cancer incidence	Age, smoking habits, and length of education		1.01	0.94-1.08
French PAARC Study							
Filleul, 2005	France	Total Suspended Particulate (exceedance frequency of 200 μg/m3)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education	14,284	0.97	0.94-1.01
		Black Smoke (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.93-1.01
		NO (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.94-1.01
		NO_2 (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.85-1.10
		SO_2 (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.99	0.92-1.07
GENAIR Cohort Study							
Vineis, 2006	Ten European Countries	PM10 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment,	197 cases	0.91	0.70-1.18

				country, occupational index and cotinine	556 controls		
		NO_2 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.14	0.78-1.67
		SO_2 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.08	0.89-1.30
		Proximity of residence to major road (exposed vs. nonexposed)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.31	0.82-2.09
Netherlands Cohort Study on Diet and Cancer							
Beelen, 2008	Netherlands	Black smoke concentration	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status	40,114	1.47	1.01-2.16
		Traffic intensity on nearest road	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status		1.11	0.88-1.41
		Living near a major road	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status		1.55	0.98-2.43
Brunekreef, 2009	Netherlands	Black smoke (per 10 μg/m3)	Lung Cancer Mortality	Age, sex, smoking status, area-level socioeconomic status	120,000	1.03	0.88-1.20
		Traffic intensity (increase of 10,000 motor vehicles/day)	Lung Cancer Mortality	Age, sex, smoking status, area-level socioeconomic status		1.07	0.96-1.19
		Black smoke (per 10 μg/m3)	Lung Cancer Incidence	Age, sex, smoking status, area-level socioeconomic status		1.47	1.01-2.16
Diet, Cancer and Health cohort study							
Raaschou-Nielsen, 2011	Denmark	**NO_x** at **residence** (per 100 μg/m3 increase)	Lung Cancer Incidence	Age, smoking, ETS, length of school attendance, fruit intake, and employment	52,970	1.09	0.79-1.51
		Traffic load at residence (per 10^4 vehicle km/day)	Lung Cancer Incidence	Age, smoking, ETS, length of school attendance, fruit intake, and employment	52,970	1.03	0.90-1.19
Three Prospective Cohorts							
Raaschou-Nielsen, 2010	Denmark	$NOx^{\int}$ (30-72 μg/m3 vs. <30 μg/m3)	Lung Cancer Incidence	Smoking (status, duration, and intensity), educational level, body mass index, and alcohol consumption.	679 cases 3481 controls	1.30	1.07-1.57
		NOx (>72 μg/m3 vs. <30 μg/m3)	Lung Cancer Incidence	Smoking (status, duration, and intensity), educational level, body mass index, and alcohol consumption.		1.45	1.12-1.88

OTHER STUDIES							
Pope, 1995	USA	Most vs. Least polluted: Sulphates	Lung Cancer mortality	Smoking	552,138	1.15	1.09-1.22
		Most vs. Least polluted: Fine particles	Lung Cancer mortality	Smoking		1.17	1.09-1.26
Yorifuji, 2010	Japan	NO_2 (10 microg/m3 increase)	Lung Cancer mortality - non smokers	Smoking	14,001	1.3	0.85-1.93
Katanoda, 2011	Japan	PM2.5 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.24	1.12-1.37
		NO2 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.26	1.07-1.48
		SO2 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.17	1.10-1.26
Hales, 2011	New Zealand	PM10(1microg/m3 increase)	Lung Cancer mortality	Age, sex, ethnicity	1 050 222	1.015	0.004-1.026

Table 2 – Results on the association between air pollution and 1-OHP in the urine of exposed individuals: linear regression, logistic regression, and correlation analyses.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 541)	Subject desription	P
Castaño-Vinyals, 2004	Review	B[a]P	Not applicable	r: 0.76	17	Pairs of data - log transformed means - from different studies	0.038
Hansen, 2004	Copenhagen, Denmark	B[a]P†		r: 0.83		personal sampling of B(a)P: mean values	0.04
		Environmental pollution	Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	OR†: 1.51 (male) / 1.38 (female)	60 88	bus drivers mail carriers	0.08
Hansen, 2005	Denmark	Residence in urban vs. rural areas	Gender, time spent outside	OR: 1.29	102 100	children in Copenhagen children from rural residences	0.03
		One additional hour spent outside/day	Gender, residence	OR: 1.58	102 100	children in Copenhagen children from rural residences	<0.001
Freire, 2009	Granada, Spain	NO2 (predicted)	Exposure to ETS† and cooking appliance	β: 0.401	93 81	children with predicted exposure to NO2≥22.50 $\mu g,m^{-3}$ / children with predicted exposure to NO2<22.50 $\mu g,m^{-3}$	0.006
Hu, 2011	Taiwan	Residence near a coal fired power plant (PAH in air)	Age, gender, ETS, dietary exposure, and traffic	OR: 1.85 95%CI(1.43, 2.40)	146	Children in high exposure community 1 vs, Low exposure community 1	
				OR: 1.65 95%CI(1.30, 2.09)	88	Children in high exposure community 2 vs, Low exposure community 1	NA

≠ r = correlation coefficient; β = =linear regression coefficient (change in 1-OHP levels (7icromole/mol) for every unit change in exposure); OR = logistic regression odds ratio
† B[a]P Benzo [a] Pyrene; OR odds ratio; ETS environmental tobacco smoke.

Table 3 – Results on the association between air pollution and 1-OHP in the urine of exposed individuals: comparison of means analysis.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 742)	Mean (micromol/mol) ± SD (unless otherwise stated)	P
Ruchirawa, 2002	Bangkok, Thailand	Environmental air pollution	Smoking	Traffic policemen 41 Office policemen 40	0.181±0.078 0.173±0.151	 0.044
Hansen, 2004	Copenhagen, Denmark	Environmental pollution	Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	Bus drivers – all 117samples Mail Carriers – all 93samples	0.19 (Range: 0.05-1.60) 0.11 (Range: 0.02-0.75)	 <0.001
			Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	Mail carriers Working outdoors 56samples Mail Carriers Working indoors 37samples	0.14 (Range: 0.02-0.75) 0.08 (Range: 0.02-0.57)	 <0.001
Tuntawiroon, 2007	Bangkok and Chonburi, Thailand	PAH† from traffic related sources	Age and lifestyle (i.e. ETS†,diet, transportation, medication etc.)	Bangkok schoolchildren 115 Group matched provincial school children – Day 0 69	0.18±0.01 0.1±0.01	 <0.0001
				Bangkok schoolchildren Day 1 115 Group matched provincial school children – Day 1 69	0.22±0.02 0.12±0.01	 <0.0001
Freire, 2009	Granada, Spain	Residence in urban vs. rural areas	Exposure to ETS† and cooking appliance	4yr old children living in urban 118 4yr old children living in rural areas 56	0.060 ± 0.040 0.054 ± 0.055	 0.20
Martinez-Salinas, 2010	Mexico	Traffic related air pollution	NA	Children in area with low vehicular traffic 39 Children in area with high vehicular traffic 17 Children in all communities of the study 258	0.8 ± 0.2 0.2 ± 0.2	<0.05 >0.05 *P-values compared to children from all communities
Hu, 2011	Taiwan	Residence near a coal fired power plant (PAH in air)	NA	High Exposure Community -1 146 High Exposure Community -2 88 Low Exposure Community -1 86 Low Exposure Community -2 49	0.186 ± 0.148 0.194 ± 0.143 0.113 ± 0.082 0.122 ±0.089	 NA

† PAH polycyclic aromatic hydrocarbons; ETS environmental tobacco smoke.

Table 4 – Results on the association between air pollution and DNA adducts in exposed individuals; linear regression, logistic regression and correlation analyses

First author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 1787)	Subject desription	P
Binkova, 1995	Czech Republic	Outdoor air pollution – individual PAH†	Age, active and passive smoking, consumption of fried or smoked food, job category	r: 0.541	21	Non smoking women working outdoors up to 8 hours – gardeners or postal workers	0.016
Whyatt, 1998	Krakow, Poland	Ambient pollution at mother's place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH & other organics	β: 1.77	19	mothers not employed away from home	0.05
		Ambient pollution at place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH and other organics.	β: 1.73	23	newborns of mothers (high pollution / low pollution group)	0.03
Sørensen, 2003	Copenhagen	Personal PM2.5	Smoking, diet, season	ß=-0.0035	75	Students monitored 4 seasons of a year	0.31
Castaño-Vinyals, 2004	Review	B[a]P† (stationary meas.)	Not applicable	r: 0.6	12	pairs of data	0.038
Peluso, 2005	10 European countries	O_3† levels	Age, gender, educational level, country and batch	β: 0.066	564	EPIC cohort subjects	0.0095
Neri, 2006	Review	Environmental pollutants (including ETS† exposure)	Not applicable	Not applicable	178	Newborns – 17yr olds 2 studies in total – 2 with statistically significant results	Not applicable
Pavanello, 2006	North-East Italy	B[a]P indoor exposure	Smoking, diet, area of residence, traffic near house, outdoor exposure	β: 0.973	457	municipal workers (non smoking)	0.012
Palli, 2008	Florence City, Italy	PM10† (from high traffic stations)	Smoking	r: 0.562	16	traffic exposed workers	0.02
Peluso, 2008	Thailand	Industrial estate residence	Smoking habits, age, gender	OR†: 1.65	72 50	Industrial estate residents control district residents	<0.05
			Smoking habits, age, gender	OR: 1.44	64 72	PAH exposed workers industrial estate residents	<0.05
Pavanello, 2009	Poland	1-pyrenol	NA†	r: 0.67	92	coke oven workers and controls	<0.0001
Pedersen, 2009	Copenhagen, Denmark	Residential traffic density	ETS†, use of open fireplace, pre-pregnancy weight, folate levels, vitamin B12 levels, maternal education and season of delivery	β: 0.6 / 0.7	75 /69	Women /umbilical cords	<0.01
Garcia-Suastegui, 2011	Mexico City, Mexico	PM2.5	Various risk alleles	r: NR	92	Young adults living in Mexico City	0.013
		PM10	Various risk alleles	r: NR	92	Young adults living in Mexico City	0.035
Herbstman, 2012	USA	PAH exposure – measured in both air and urine	NA	r: NR	NR	152 participants – prenatal exposure, DNA adducts in cord blood	Not significant

≠ r = correlation coefficient; β =linear regression coefficient (change in DNA adduct levels (adducts/10^8 nucleotides) for every unit change in exposure); OR = logistic regression odds ratio
† PAH polycyclic aromatic hydrocarbons, PM10 particulate matter of diameter less than 10 microns; B[a]P Benzo [a] Pyrene; O_3 ozone; NA not available; ETS environmental tobacco smoke; OR odds ratio

Table 5 – Results on the association between air pollution and DNA adducts in exposed individuals; comparison of means analysis.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 1044)	Mean adducts/ 10^8 nucleotides ± SD (unless otherwise stated)	P
Perera, 1991	Poland	Environmental air pollution	NA†	Residents in industrial area 20	30.4±13.5	
				Rural controls 21	11.01±22.6	<0.05
Hemminki, 1994	Stockholm, Sweeden	Traffic related air pollution	Age, smoking	Bus drivers – urban routes 26	0.9 ± 0.35	Non sig.
				Bus drivers – sub urban routes 23	1.4 ± 0.48	<0.001
				Taxi drivers – mixed routes 19	1.6 ± 0.91	<0.010
				Controls 22	1.0 ± 0.32	
Nielsen, 1996	Denmark	Environmental air pollution	Smoking, PAH† rich diet	Bus drivers in Central Copenhagen 49	Median: 1.214 Range: 0.142-22.24	
				Rural controls 60	Median: 0.074 Range: 0.003-8.876	0.001
Nielsen, 1996 (2)	Denmark and Greece	Environmental air pollution	Smoking, sex	Students in urban universities 74	Median: 0.205	
				Students in agricultural colleges 29	Median: 0.152	0.02
Yang 1996	Milan, Italy	Traffic related air pollution	Sex, age, smoking habits	News stand workers at high traffic areas 31	2.2 ± 1.0	
				News stand workers at low traffic areas 22	2.2 ± 1.2	0.27
Topinka, 1997	Teplice & Prachatice, N&S Bohemia	Residence in Industrial area	NA†	Placenta samples- industrial polluted area (winter): GSTM− genotype 15	1.49 ± 0.70	
				Placenta samples –agricultural area (winter): GSTM− genotype 17	0.96 ± 0.55	0.027
Merlo, 1997	Genova, Italy	Ambient PAH concentrations	NA†	Traffic police workers 94	1.48 ± 1.35	
				Urban residents 52	1.01 ± 0.63	0.007
Ruchirawa, 2002	Bangkok, Thailand	Environmental air pollution	Smoking, sex	Traffic Policemen 41	1.6±0.9	
				Office duty policemen 40	1.2±1.0	0.03
Marczynski, 2005	Germany	PAH in air (ambient and personal monitoring)	NA†	Samples from 16 workers(increased PAH exposure)	Range: 0.5 – 1.19Range: <0.5 –	
				Samples from 16 workers¥ (reduced PAH exposure)	0.09	<0.0001
Topinka, 2007	Prague, Czech Republic	c-PAH† (personal exposure)	Smoking, ocuupational duration	109 policemen – January (highest exposure)	2.08±1.60	
				109 policemen – March	1.66±0.65	<0.0001
Tuntawiroon, 2007	Bangkok and Chonburi, Thailand	c-PAH and B[a]P†	Age and lifestyle (i.e. ETS†, transportation, medication, diet etc.)	Bangkok schoolchildren 115	0.45±0.03	
				Provincial school children (group matching) 69	0.09±0.00	<0.0001
Fanou, 2011	Cotonou, Benin	Environmental air pollution	NA†	Taxi-motorbike drivers 13	24.6±6.4	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Street food vendors 16	34.7±9.8	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Gasoline salesmen 20	37.2±8.1	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Street side residents 11	23.78±6.9	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	

† N/A not applicable; NA not available; PAH polycyclic aromatic hydrocarbons; c-PAH carcinogenic polycyclic aromatic hydrocarbons; B[a]P benzo [a] pyrene; ETS environmental tobacco smoke
¥ The sample sizes reported in the summary tables refer to subjects with measurments available both before and after change in work conditions

Table 6 - Results on the association between air pollution and oxidatively damaged nucleobases/deoxynucleosides in urine or mononuclear blood cells; comparison of means analysis

First author, Year	Area, country	Exposure definition/source Referents' definition	Biomarker	Groups Sample size (Total: 2827)	Level (Mean ± SD, unless otherwise stated)	Controlled confounders
Suzuki 1995	Japan	Sampling before and after a stay in a street	8-oxoGua in urine (HPLC-ECD)	3	After:9.9±2.5 Before: 4.22±2.0 (pooled data from several timepoints 0-24 after exp.)	Cross-over study
Calderon-Garciduenas 1999	Mexico	Children in urban and low-polluted area	8-oxodG in nasal epithelial cells (immunohistochemistry)	Exposed: 86 Controls: 12	602 ± 195* 210 ±122	NA†
Autrup 1999; Loft 1999	Copenhagen, Denmark	Bus drivers in the city center and rural/suburban controls	8-oxodG in urine (HPLC-ECD)	Exposed: 29 Controls:20	1.74 ± 4,69 1.54 ± 4.29	Age, BMI†, metabolic and DNA repair phenotype
Staessen 2001	Belgium	Adolescents from industrial and rural areas	8-oxodG in urine (HPLC-ECD)	Peer: 100 Wilrijk: 42 Hoboken: 58	0.44 (0.40-0.48) 0.57 (0.49-0.66)* 0.49 (0.42-0.56) Geometric mean and 95% CI	Sex, smoking
Chuang 2003	Taiwan	Taxi-drivers and controls	8-oxodG in urine (ELISA)†	Exposed: 95 Controls: 75	0.33± 0.20* 0.20 ± 0.14	Age, education, exercise
Lai 2005	Taipei city, Taiwan	Highway toll station workers and controls	8-oxodG in urine (ELISA)	Exposed: 47 Controls: 24	13.3±7.1* 8.4±6.2	Age, smoking
Harri 2005	Finland	Garage/waste workers and controls	8-oxodG in urine and MNBC (HPLC-ECD)	**Urine:** Exposed: 29 Controls: 36 **MNBC:** Exposed: 19 Controls: 18	Winter: 1.52 ± 0.44 1.56 ± 0.61 Summer: 1.61±0.33 1.43±0.4 4.84± 0.17 4.11 ±0.16	Age, smoking, BMI
Vinzents 2005	Copenhagen, Denmark	Sampling after cycling in traffic-intense streets or laboratory	FPG sites in MNBC	15	Traffic: 0.08 (0-0.04)* Lab: 0.02 (0-0.04)	Cross-over study
Avogbe 2005	Rep. of Benin	Subjects from urban and rural areas	FPG sites in MNBC	Taximoto: 24 Roadside: 37 Suburban: 42 Rural: 27	1620 ± 310* 1250 ± 198* 1110 ± 188* 650 ± 160	Metabolic genes
Fanou 2006	Rep. of Benin	Taxi-moto drivers and controls	8-oxodG in MNBC (HPLC-ECD)	Exposed: 35 Controls: 6	2.05±1.25* 1.11±0.82	NA†
Cavallo 2006	Italy	Airport personnel and controls	FPG sites in MNBC	Exposed: 41 Controls: 31	55.86 ± 12.85* 43.01 ± 7.97	Age, smoking, dietary habits
Bräuner 2007	Copenhagen, Denmark	Sampling before and after controlled exposure to street PM	FPG sites in MNBC	29	Air: 0.53 (0.37-0.65)* FA†:0.38 (0.31-0.53) Median and quartiles	Age, sex, smoking, CVD†, BMI
Singh 2007	Prague (Czech Rep.) Kosice (Slovakia) Sofia (Bulgaria)	City policemen, bus drivers and controls	8-oxodG (LC-MS/MS) M_1dG (immunoslot blot) In MNBC	Exposed: 98 Controls: 105 Exposed: 198 Controls: 156	33.0±30.1 29.2±21.2 58.3±37.5 49.2±30.3	Smoking, demographic variables, diet
Novotna 2007	Prague, Czech Rep.	Policemen and controls sampled in different seasons	ENDOIII/FPG sites in MNBC	Exposed: 54 Controls: 11	Jan: 2.91± 1.84* Sep: 2.12 ± 1.62 Jan:1.36± 1.53 Sep: 1.22 ± 0.96	Metabolic and DNA repair genotypes
Rossner, Jr. 2007,	Prague, Czech Rep.	Bus drivers and controls sampled in	8-oxodG in urine	Exposed: 50	7.59 ± 2.25*	Medical history, lifestyle

2008		there different seasons	(ELISA)		6.73 ± 2.48* 5.67 ± 2.50*	
				Controls: 50	6.29 ± 2.59 5.51 ± 2.36 3.82 ± 1.73	
Buthbumrung 2008	Thailand	Schoolchildren in Bangkok and rural controls	8-oxodG in leukocytes and urine (HPLC-ECD)	Exposed: 40 Controls: 32	0.25 ± 0.13 0.08 ± 0.34	Metabolic genes
				Exposed 43 Controls: 32	2.16 ± 1.84 1.32 ±1.24	
Danielsen 2008	Sweden	Sampling before and after controlled exposure to wood smoke	8-oxodG 8-oxoGua in urine: HPLC-GC/MS FPG sites in MNBC	13	16.4% (95% CI: -6.9,45.5) 79.3% (95% CI -12.9,269) -15% (95% CI:-31.1,4.9)	Cross-over study
Palli 2009	Florence, Italy	Metropolitan area	FPG sites in MNBC	Exposed 44 Controls: 27	5.0 ± 3.06 4.11 ± 3.96	Sex, smoking, season
Svecova 2009	Teplice and Prachatice (Czech Rep.)	Children	8-oxodG in urine (ELISA)	Teplice: 495 Prachatice:399	14.6 (3.1-326.5) 15.2 (3.0-180.8)	Ethinicity, mothers smoking, education, sex, age, atopic diseases
Bagryantseva 2010	Praque, Czech Rep.	Bus drivers, garage men and office workers	8-oxodG in urine (ELISA)	Bus drivers: 50 Garage men: 20 Controls: 50	5.67 ± 2.5* 6.54 ± 6.9* 3.82 ± 1.73	Age, vitamins, plasma lipids, metabolic and DNA repair genes
			EndoIII/Fpg sites in lymphocytes	Bus drivers: 50 Garage men: 20 Controls: 50	2.35 ± 2.17 2.56 ± 2.52 2.55 ±2.86	
Han 2010	Taiwan	Bus drivers and office workers	8-oxodG in urine (ELISA)	Exposed: 120 Controls: 58	9.5 ± 5.7* 7.3 ± 5.4	Age, BMI, smoking. Alcohol, areca chewing, tea, coffee energy drink, exercise
Fan 2011	GuangZhou City, China	Children	8-oxodG in urine (ELISA)	Exposed: 39 Controls: 35	20.87 ± 14.42 16.78 ± 13.30	Age, sex, height, weight, passive smoking, diet, transportation tool and time taken to/from school
Rossner, Jr, 2011	Praque and Ostrava (Czech Rep.)	Policemen and office workers	8-oxodG in urine (ELISA)	Ostrava: 75 Praque: 65	4.28 ± 2.27 4.84 ± 1.61	Age, passive smoking, cotinine, plasma lipids, vitamins, DNA repair gens

† BMI body mass index; NA not available; CVD cardiovascular disease; ELISA enzyme-linked immunosorbent assay**;** FA filtered air

Table 6a. Confounding in studies of DNA adducts

Adjustment	Number of studies	References
Several relevant confounders including smoking but not diet	**7**	**Hemminki 1994, Nielsen 1996, Peluso 2005, Peluso 2008, Ruchirawa 2002, Topinka 2007, Yang 1996,**
Several relevant confounders including smoking including diet	**7**	**Binkova 1995, Nielsen 1996 (2), Pavanello 2006, Pedersen 2009, Sorensen 2003, Tuntawiroon 2007, Whyatt 1998,**
Smoking	**1**	**Palli 2008**
Various Risk Alleles	**1**	**Garcia-Suastegui 2011**
Confounding not relevant	**1**	**Marczynski 2005**
No information about confounding factors	**6**	**Ayi Fanou 2011, Herbstman 2012, Merlo 1997, Pavanello 2009, Perera 1991, Topinka 1997**

Table 7 - Results on the association between air pollution and oxidatively damaged nucleobases/deoxynucleosides in urine or mononuclear blood cells; linear regression and correlation analysis

First author, year	Area, country	Exposure definition/source	Biomarkers and methods	Sample size (Total: 1642)	Effect Measure≠	Controlled confounders
Lagorio 1994	Rome Italy	Filling station attendants	8-oxodG in urine (HPLC-ECD)	65	r = 0.34* (benzene)	Age, length of employment, smoking, exposure to X-ray
Sørensen 2003a	Copenhagen, Denmark	Students living in the metropolitan area	8-oxodG (HPLC-ECD) in urine and MNBC		β = 0.010* (8-oxodG, lymphocytes) β = -0.007 (8-oxodG, urine)	Season, sex, outdoor temperature
			FPG/EndoIII sites in MNBC	50	β = 0.0025 (EndoIII) β = 0.014 (FPG)	
Sørensen 2003b	Copenhagen, Denmark	Healthy subjects living in the metropolitan area	FPG/EndoIII sites in MNBC 8-oxodG (HPLC-ECD) in urine and MNBC	40	r_s = 0.39* Non-significant	Smoking, type of work, sex, genotype (metabolism)
Vinzents 2005	Copenhagen, Denmark	Sampling after cycling in traffic-intense streets or laboratory	FPG sites in MNBC	15	$\beta=1.5x10^{-3}$ per ultrafine particle time weighted exposure unit	Cross-over study
Bräuner 2007	Copenhagen, Denmark	Sampling before and after controlled exposure to street PM	FPG sites in MNBC	29	NC_{12}†: β = -0.033 NC_{23}: β =0.066* NC_{57}: β=0.040*	Age, sex, smoking, CVD†, BMI† included in model
Chuang 2007	Taipei, Taiwan	College students living in the metropolitan area	8-oxodG in plasma (ELISA)	76	PM10: -9.2%, (95% CI: -21.5;3.2) PM2.5: -5.0% (95% CI: -14.3-4.4) O3: 2.2% (95% CI: 0.9;3.5)	Sex, age, BMI, weekday, temperature, relative humidity
De Coster 2008	Flanders, Belgium	Industrial and urban areas	8-oxodG in urine (ELISA)	399	β = 0.179 (95% CI: 0.077-0.282) with 1-OHP as biomarker of internal exposure	Age, Sex, recent smoking
Svecova 2009	Teplice&Prachatice (Czech Rep.)	Children living in the two areas	8-oxodG in urine (ELISA)	Teplice: 495 Prachatice:399	β=0.16* (air pollutants)	Ethinicity, mothers smoking, education, sex, age, atopic diseases
Allen 2009	Washington, USA	Subjects with MetS with controlled exposure to diesel exhaust	8-oxodG in urine (ELISA) †	10	β = 0.087 (95% CI: -0.13; 0.31)	Cross-over study
Kim 2009	Boston, USA	Subjects with hypertension and controls (panel study)	8-oxodG in urine (ELISA)	21	β=-0.60 (hypertensive) β=1.1 (controls)	Age, sex, smoking, time of the day
Bagryantseva 2010	Praque, Czech Rep.	Bus drivers, garage men and office workers	8-oxodG in urine (ELISA)	120	β= 0.105 /BaP β= 0.026 (PAH)	Age, vitamins, plasma lipids, metabolic and DNA repair genes
			EndoIII/FPG sites in lymphocytes	120	β=-0.62 (BaP) β=-0-056 (PAH)	
Lee 2010	Taiwan	Inspection station workers and controls	8-oxodG in urine (ELISA)	Exposed:11 Controls: 32	β=7.47 (SE = 3.3)*	Smoking, cooking at home
Fan 2011	GuangZhou City, China	Children in a kindergarten	8-oxodG in urine (ELISA)	74	r=0.055 (OH-PAH)	Age, sex, height, weight, passive smoking, diet, transportation to/from kindergarten
Mori 2011	Tokyo	Children in a kindergarten	8-oxodG in urine (ELISA)	76	β=0.216 (Ln(1-OHP))	Age, sex, Mn, As, vitamin A, vitamin C, cotinine
Ren 2011	Boston, USA	Eldery subjects	8-oxodG in urine (ELISA)	320	PM2.5: 30.8% (95% CI: 9.3-52.2)	Age, BMI, smoking, vitamins
Rossner, Jr 2011	Praque, Czech Rep.	Policemen	8-oxodG in urine (ELISA)	59	β= 0.04* (PM2.5 stationary monitoring station) β=0.16 (BaP) β=-0.02 (PAH)	Age, cotinine, cholesterol, triglycerides

≠ r = correlation coefficient; β = linear regression coefficient (change in levels of oxidatively damaged nucleobases for every unit change in exposure); % per cent difference
† MetS metabolic syndrome; ELISA enzyme-linked immunosorbent assay; BMI body mass index; CVD cardiovascular disease, $NC_{size\ cut\ off}$ Number concentration.

Table 7a. Confounding in studies of oxidative damaged to nucleobases in blood or urine

Adjustment	Number of studies	References
Several relevant confounders including smoking	**23**	**Autrup 1999, Brauner 2007, Cavallo 2006, Chuang 2003, Chuang 2007, De Coster 2008, Fan 2011, Han 2011, Harri 2005, Kim 2009, Lagorio 1994, Lai 2005, Lee 2010, Loft 1999, Palli 2009, Ren 2011, Rossner 2007, Singh 2007, Sorensen 2003a, Sorensen 2003b, Staessen 2001, Svecova 2008, Svecova 2009**
Metabolic and/or DNA repair gene polymorphisms	**5**	**Avogbe 2005, Bagryantseva2010, Buthbumrung 2008, Novotna 2007, Rossner 2011**
Confounding not relevant	**4**	**Allen 2009, Danielsen 2008, Suzuki 1995, Vinzents 2005,**
No information about confounding factors	**2**	**Ayi Fanou 2006, Calderón-Garcidueñas 1999,**

Table 8 – Results on the association between air pollution and CAs in the cells of exposed individuals; logistic regression and comparison of means analyses.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 1265)	Mean (% frequenciesΔ) ± SD	P
Knudsen, 1999	Copenhagen, Denmark	Air pollution (urban)	Metabolic genotypes, DNA repair, age, sex	office workers 41	2.46 ± 1.98	
				postal workers 60	2.12 ± 1.38	Not significant
				Bus drivers – high exposure 55	2.84 ± 1.87	
				Bus drivers – low + medium exposure 45	2.24 ± 1.57	Not significant
Sram 1999	Czech Republic	Urban air pollution	Maternal height and pre-pregnancy weight, parity, marital status, education and maternal smoking, season and the year of the study	Pregnant Mothers: Industrial + residential heating (Teplice) 131	1.54 ± NA†	
				Pregnant Mothers: Residents in agricultural districts (Prachatice) 48	1.04 ± NA†	<0.05
Kyrtopoulos, 2001	Athens and Halkida, Greece	Air pollution (in city of studying)	Smoking	Students in Athens (higher PAH† exposure & lower PM2.5† exposure) 222	0.88±0.97	
				Students in Halkida (lower PAH exposure & higher PM2.5 exposure) 149	1.06±1.12	Not significant
Burgaz, 2002	Ankara, Turkey	Air pollution (traffic related)	Age, sex, smoking habits	Traffic policemen 18	1.29±0.30	
				Control group 5	0.26±0.14	<0.05
				Taxi drivers 29	1.82±0.34	
				Control group 5	0.26±0.14	<0.01
Sram, 2007	Prague, Czech Republic	c-PAHs† on respirable air particles (<2.5 m)	Smoking, medical histories	Sampling in January: higher PM† and PAH exposures 61	0.27±0.18	
				Sampling in March: lower PM and PAH exposures 61	0.16±0.17	<0.001
Zidzik, 2007	Kosice (Slovakia), Prague(Cz.Republic) & Sofia (Bulgaria)	cPAH	Sex	Exposed policemen in Kosice 51	2.6±2.64	
				Controls in Kosice 55	2.14± 1.61	Not significant
				Exposed policemen in Prague 52	2.33±1.53	
				Controls in Prague 50	1.94±1.28	Not significant
				Exposed policemen in Sofia 50	3.04±1.64	
				Controls in Sofia 45	1.79±0.77	<0.05
				Exposed bus drivers in Sofia 50	3.6±1.63	
				Controls in Sofia 45	1.79±0.77	<0.05
Balachandar, 2008	Tamilnadu, India	ETS†	Age	Group I : <6hrs exposure/day and <30yrs old		
				Passive smokers 18	5.00 ± 1.68,	
				Controls 18	1.16 ± 0.92,	Significant
				Group II : >6hrs exposure/day and >30yrs old		
				Passive smokers 25	9.04 ± 3.73	
				Controls 25	2.76 ± 2.12.	Significant
Rossnerova, 2011	Prague and Ceske Budejovice, Czech Republic	Air pollution (urban vs. rural)	Sex	Mothers in Prague (urban) 86	0.80 ± 0.27	<0.001
				Mothers in Ceske Budejovice (rural) 92	0.61 ± 0.21	
					Linear Regression Coefficient (95% CI)	
Garcia-Suastegui, 2011	Mexico City, Mexico	Air pollution – PM10	Unadjusted	91 individuals sampled during dry season	NA	0.669
		Air pollution – PM2.5				0.399
		Air pollution – PM10	Unadjusted	80 individuals sampled during rainy season	NA	0.709
		Air pollution – PM2.5				0.843
					Logistic regression OR$^{\infty}$ (95% CI)	
Rossner, 2011	Prague and Ostrawa, Czech Republic	Air pollution at residence	Age, benzene exposure, cotinine plasma levels, total, HDL, and LDL cholesterol levels, triglycerides, Vitamins a, C and E in plasma and various gene expressions	Subjects in Prague (less polluted) 64		
				Subjects in Ostrawa (more polluted) 75	0.18 (0.05-0.67)$^{\infty}$	0.010

† NA not available; PAH polycyclic aromatic hydrocarbons; PM2.5 particulate matter with dimater less than 2.5 microns; N/A not applicable; c-PAH carcinogenic polycyclic aromatic hydrocarbons; ETS environmental tobacco smoke.

Δ Percentage of cells with chromosomal aberrations

$^{\infty}$ Odds ratio of having chromosomal aberrations above median, for subjects in Prague compared to subjects in Ostrawa

Table 9 – Results on the association between air pollution and MN in peripheral blood cells of exposed individuals: linear regression analyses

First Author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 1478)	Subject desription	p
Neri, 2006	Review	Environmental Pollutants	Not applicable		1071	Children: 1-16 yrs old 4 studies in total – 4 with statistically significant results	
Ishikawa, 2006	Shenyang city, China	Air pollution (ambient)	Smoking habits, sex, age, metabolic enzyme and DNA repair gene polymorphisms	β: 1.57	66 63	Female industrial Female rural residents	<0.05
Pedersen, 2009	Copenhagen, Denmark	Residential traffic density (validated by indoor levels of nitrogen dioxide and PAH)	ETS exposure, use of open fireplace, prepregnancy weight, folate levels, vitamin B12 levels, maternal education and season of delivery	β: -0.1 β: 0.4	75 69	Women Umbilical cords	0.02
				Mean (% frequencies) ± SD			
Merlo, 1997	Genova, Italy	Ambient PAH concentrations	Sex	3.73 ± 1.6 4.03 ± 1.61	82 52	Traffic police workers Urban residents	0.38
Rossnerova, 2011	Prague and Ceske Budejovice, Czech Republic	Air pollution (urban vs. rural)	Sex	8.35 ± 3.06 6.47 ± 2.35	86 92	Mothers in Prague (urban) Mothers in Ceske Budejovice (rural)	<0.001

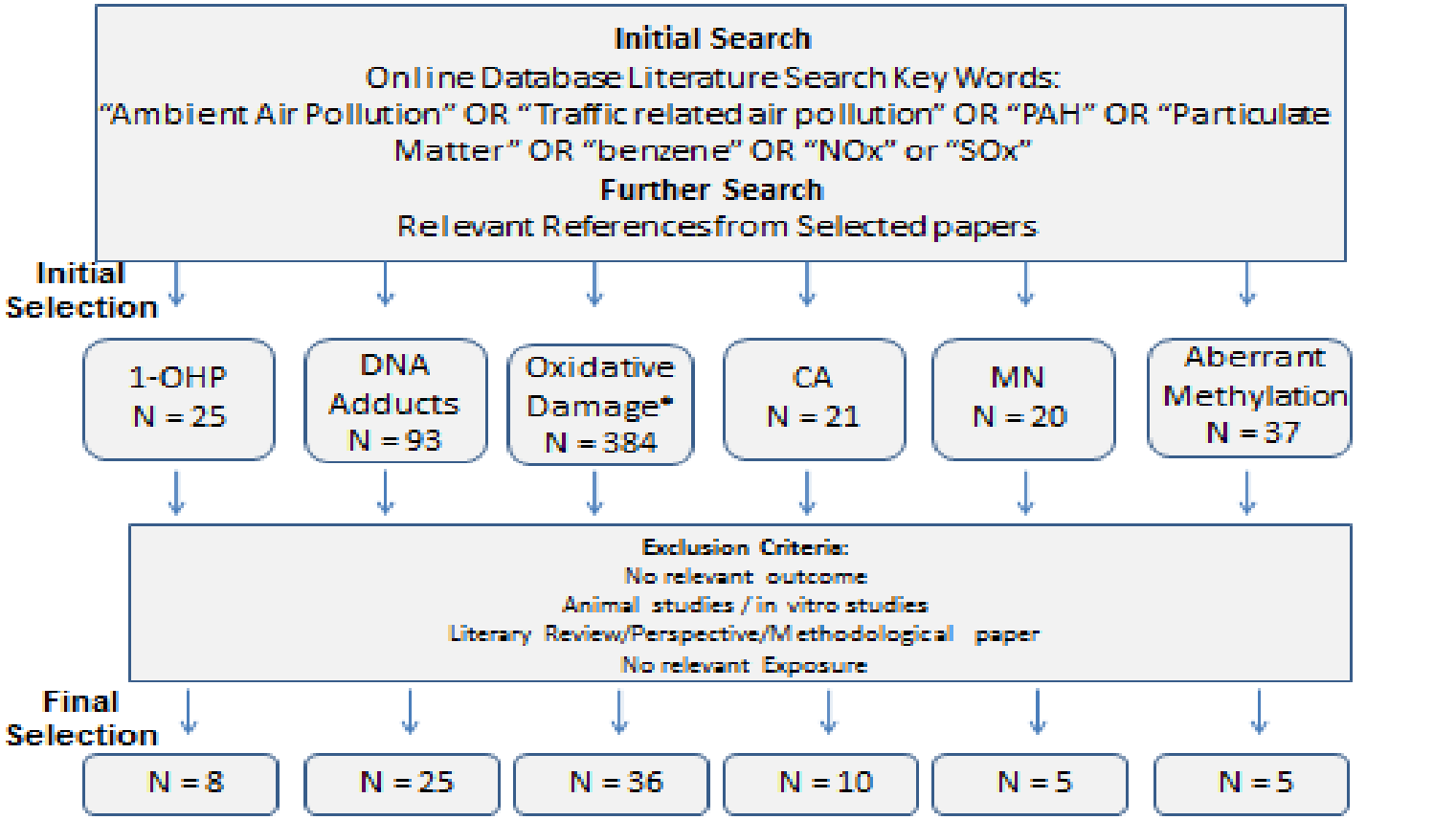
≠ β = linear regression coefficient (change in micronuclei frequencies (frequency per 1000 cells) per unit change in exposure)
† PBLs peripheral blood lymphocytes; N/A not applicable; PM10 particulate matter with dimater less than 10 microns; polycyclic aromatic hydrocarbons.

Table 10 - Results on the association between air pollution and methylation changes in the cells of exposed individuals.

First author, Year	Area/ Country	Exposure	Outcome	Controlled Confounders	Effect Measure≠	CI†	Sample Size (Total: 1499)	Subject desription	P
Baccarelli, 2007	Boston, USA	Ambient Black Carbon (hourly concentrations measured at a monitoring site approximately 1 km from the site of examination (7 day mean))	LINE-1 methylation	Multiple clinical and environmental covariates	r: -0.11	(-0.18) (-0.04)	718	subjects from the Normative Aging Study	0.002
		Ambient Black Carbon (hourly concentrations measured at a monitoring site approximately 1 km from the site of examination (7 day mean))	Alu methylation	Multiple clinical and environmental covariates					Not significant
Baccarelli, 2009	Boston, USA	PM2.5† concentrations (7day mean)	LINE-1 methylation	Age, BMI, cigarette smoking, pack-years, statin use, fasting blood glucose, diabetes mellitus, percent lymphocytes, and neutrophils in differential blood count, day of the week, season, and outdoor temperature	r: -0.13	(-0.19) (-0.06)	718	subjects from the Normative Aging Study	<0.001
		PM2.5 concentrations (7day mean)	Alu methylation	Age, BMI, cigarette smoking, pack-years, statin use, fasting blood glucose, diabetes mellitus, percent lymphocytes, and neutrophils in differential blood count, day of the week, season, and outdoor temperature	r: -0.01	(-0.07) (0.05)			0.71
Tarantini, 2009	Brescia, Northern Italy	PM10 (first day of the week and after 3 days of work)	LINE-1 methylation	Unadjusted	0.02%	SE: 0.11	63	workers	0.89
		PM10 (first day of the week and after 3 days of work)	Alu methylation	Unadjusted	0%	SE: 0.08			0.99
		PM10 (first day of the week and after 3 days of work)	iNOS promoter methylation	Unadjusted	-0.61%	SE: 0.26			0.02
		PM10 (average level of individual exposure)	LINE-1 methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.34	SE: 0.09			0.04
		PM10 (average level of individual exposure)	Alu methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.19	SE: 0.17			0.04
		PM10 (average level of individual exposure)	iNOS promoter methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.55	SE: 0.58			0.34
Madrigano, 2011	New York, USA	PM2.5 (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	0.03%	(-0.12) (0.18)	706	subjects from the Normative Aging Study	Not Significant
			Alu		0.03%	(-0.07) (0.13)			Not Significant
		Black Carbon (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	-0.21%	(-0.50) (0.09)			Not Significant
			Alu		-0.31%	(-0.12) (-0.50)			P<0.05
		SO4 (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	-0.27%	(-0.02) (-0.52)			P<0.05
			Alu		-0.03%	(-0.20) (0.13)			Not Significant
Herbstman, 2012	New York, USA	PAH exposure – prenatal	Global Methylation	Ethnicity	β: -0.11	(-0.21) (0.00)	164	cord blood samples	0.05

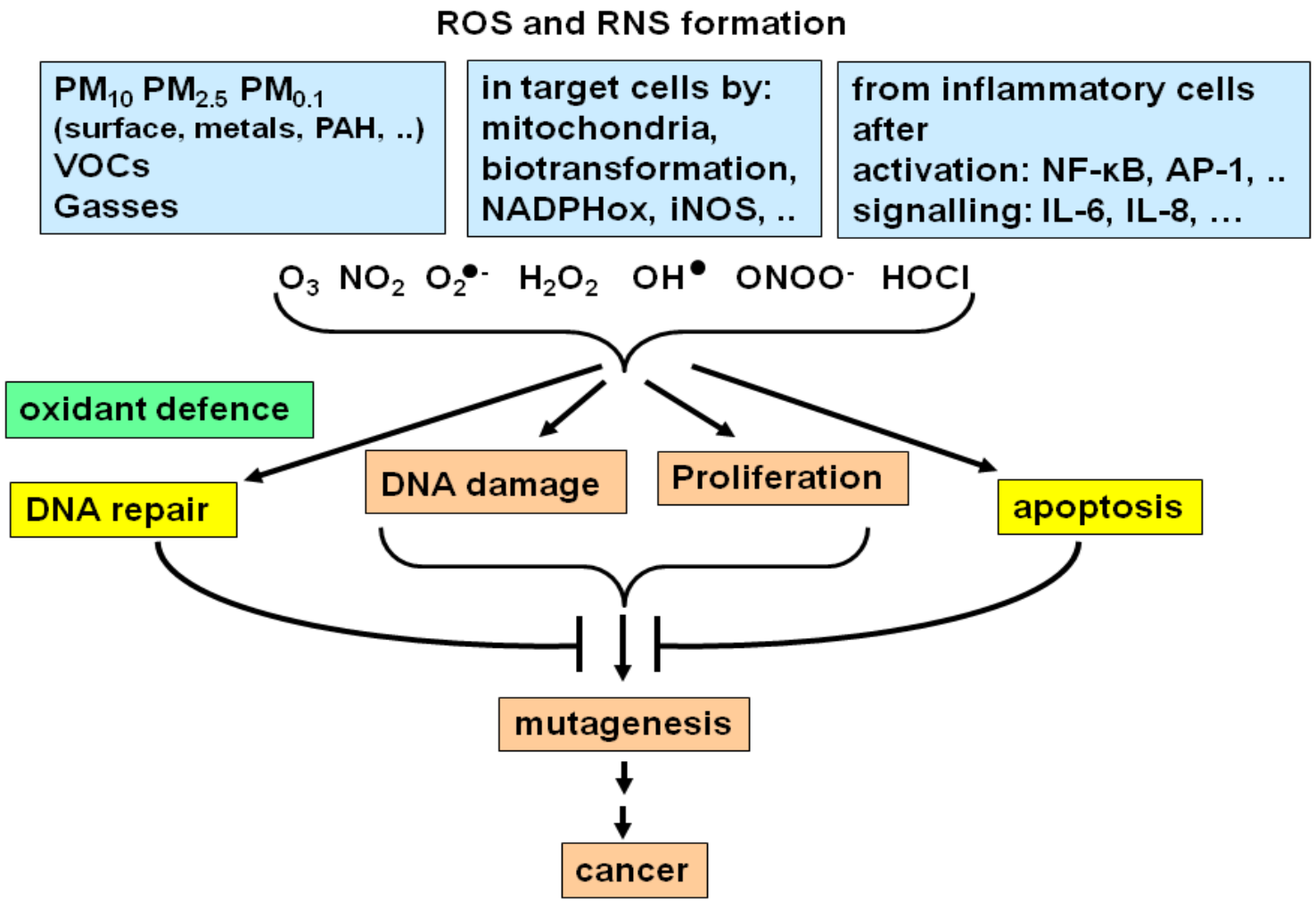
≠ r = correlation coefficient; β = linear regression coefficient (change in DNA methylation levels (**%5mC)** per unit change in exposure); % per cent difference
† CI confidence interval; LINE-1long interspersed nuclear element-1; PM10 particulate matter with diameter of less than 10 microns; tHcy total homocysteine; BMI body mass index; PM2.5 particulate matter with diameter of less than 2.5 microns; PAH polycyclic aromatic hydrocarbons.

Figure 1 - Flow Chart of Literature Review



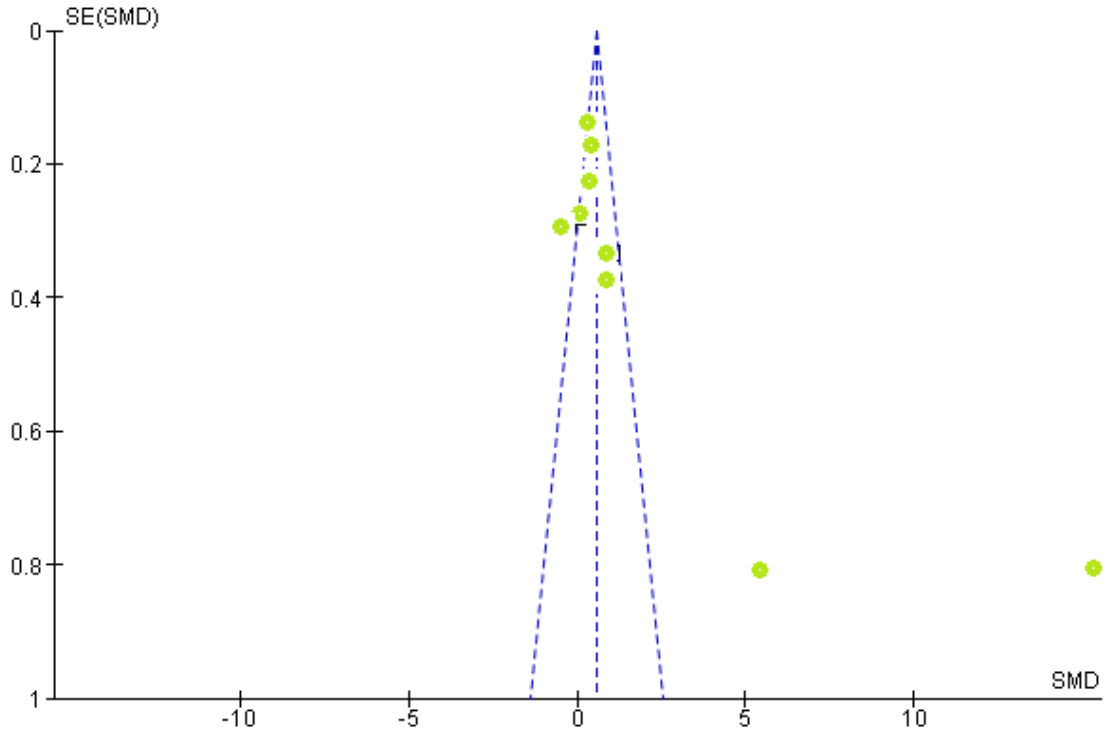
* For oxidative damage search terms also included: "diesel exhaust", "wood smoke", and "biomass".

Figure 2 – Putative Mechanisms of cancer through oxidative damage from air pollution



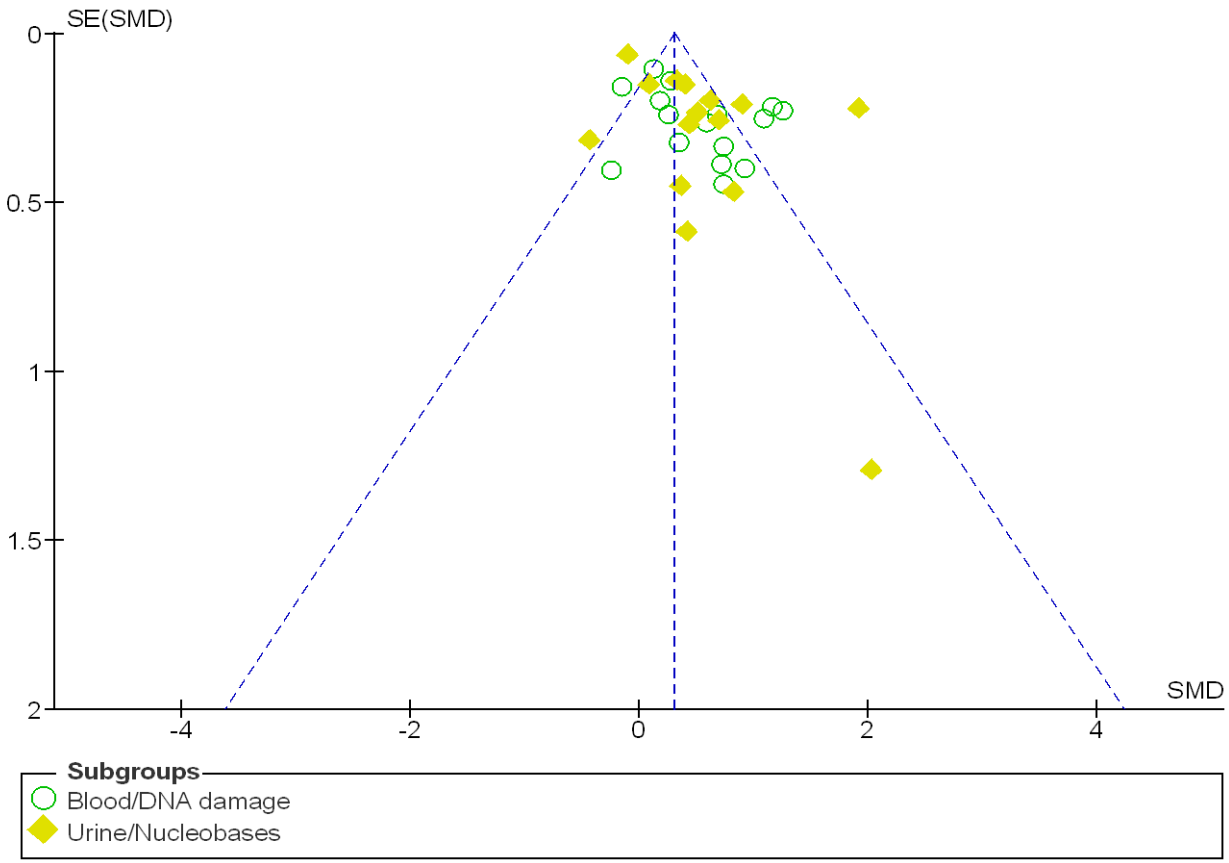
Adapted from: Risom, L, P. Møller, and S. Loft (2005) Oxidative stress-induced DNA damage by air pollution, Mutat. Res. 592:119-137

Figure 3 - Funnel plot of the standard error of the standardized mean difference (SMD) vs the SMD of studies on DNA adducts (in a fixed effects model to get the pseudo CI lines).



NOTE: Three studies not reporting means and standard deviations were excluded (Nielsen 1996a, Nielsen 1996b, Marczynski 2005).

Figure 4 - Funnel plot of the standard error of the standardized mean difference (SMD) vs the SMD of all the studies on oxidative DNA damage shown in Table 5-Supplemental Material (in a fixed effects model to get the pseudo CI lines).



In the papers without report of SD this was estimated from the data as explained in the review and meta-analysis paper of Møller and Loft P 2010 (70).

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SUPPLEMENTARY MATERIAL

Title: Biomarkers of ambient air pollution and lung cancer: strength of evidence Christiana Demetriou[1,6], Ole Raaschou-Nielsen[2] Steffen Loft[3], Peter Møller[3], Roel Vermeulen[4], Domenico Palli[5], Marc Chadeau-Hyam[1], Wei W Xun[1], Paolo Vineis[1]

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Table 1 – Prospective study results on the relationship between exposure to air pollution and lung cancer incidence and/or mortality, listed by study or cohort

First Author, Year	Area/ Country	Exposure‡	Outcome	Controlled Confounders	Number of Subjects	RR†	CI†
AMERICAN STUDIES							
American Legion Study							
Buell, 1967	USA	>10 yrs in LAcounty vs.other counties	Lung Cancer Mortality	Age, sex, smoking, size of birthplace	336,571 person-yrs	2.5	*not reported
		>10yrs vs. <10yrs in LA county	Lung Cancer Mortality	Age, sex, smoking, size of birthplace		1.26	*not reported
ASHMOG Study							
Mills, 1991	USA	Total Suspended Particulate (exceedance frequency of 200µg/m3)	Cancer in females incidence	Age, sex, education, ex-smoking, ETS†, and occupational exposure	6,000	1.72	0.81-3.65
		Ozone (exceedance frequency of 10pphm)	Lung Cancer incidence	Age, sex, education, ex-smoking, ETS, and occupational exposure		2.25	0.96-5.31
Beeson, 1998	California, USA	Ozone (100ppb increase)	Lung Cancer incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use	6,338	3.56	1.35-9.42
		PM10† (IQR increase)	Lung Cancer Incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use		5.21	1.96-13.99
		SO_2 (IQR increases)	Lung Cancer Incidence - males	Pack-years of past cigarette smoking, educational level, and current alcohol use		2.66	1.62-4.39
		PM10 exceedance frequencies of 50 microg/m3 (IQR increase)	Lung Cancer Incidence - females	Smoking, Age		1.21	0.55-2.66
		PM10 exceedance frequencies of 60 microg/m3 (IQR increase)	Lung Cancer Incidence - females	Smoking, Age		1.25	0.57-2.71
		SO_2 (IQR increases)	Lung Cancer Incidence - females	Smoking, Age		2.14	1.36-3.37
Abbey, 1999	USA	PM10 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use	6,338	3.36	1.57-7.19
		PM10 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		1.33	0.60-1.96

		Ozone (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		2.10	0.99-4.44
		Ozone (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		0.77	0.37-1.61
		SO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		1.99	1.24-3.20
		SO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		3.01	1.88-4.84
		NO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in males	Years of education, pack-years of ex smoking, alcohol use		1.82	0.93-3.57
		NO_2 (IQR increase in mean conc.)	Lung Cancer Mortality in females	Years of education and pack-years of past smoking		2.81	1.15-6.89
McDonnell, 2000	USA	PM2.5† (IQR increase = 24.3 μg/m3),	Lung Cancer Mortality		6,338	2.23	0.56-8.94
		PM2.5-10 (IQR increase = 9.7 μg/m3)	Lung Cancer Mortality			1.25	0.63-2.49
		PM10 (IQR increase = 29.5μg/m3)	Lung Cancer Mortality			1.84	0.59-5.67
American Cancer Prevention Study II							
Pope, 2002	USA	NO_2 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, smoking, education, marital status, body mass, alcohol comsumption, occupation, and diet	409-493 thousand	1.14	1.04-1.23
Jerrett, 2005	USA	PM10 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables	22,905	1.2	0.79-1.82
		Ozone (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables		0.99	0.91-1.07
		Distance to freeways (<500m vs. >500m)	Lung Cancer Mortality	Age, sex, race, education, smoking, marital status, BMI, alcohol consumption, occupational exposure, diet, and other ecological variables		1.44	0.94-2.21
Turner, 2011	USA	PM2.5 (10 microg/m3 increase) ACP	Lung Cancer Mortality	Age, sex, smoking, educational attainment, BMI, chronic lung disease	188,699	NA	1.15-1.27
Pope, 2011	USA	PM2.5 (10 microg/m3 increase)	Lung Cancer Mortality	Age, sex, education, marital status, body mass, alcohol consumption, occupational exposures, smoking duration, and diet	1.2million	1.14	1.04-1.23
Harvard Six Cities Study							
Dockery, 1993	USA	Inhalable particles:	Lung Cancer	Age, sex, smoking, education, and BMI		1.27	1.08-1.48

		Most polluted vs. Least polluted city	mortality				
					8,111		
		Fine particles: Most polluted vs. Least polluted city	Lung Cancer mortality	Age, sex, smoking, education, and BMI		1.26	1.08-1.47
		Sulphate particles: Most polluted vs. Least polluted city	Lung Cancer mortality	Age, sex, smoking, education, and BMI		1.26	1.08-1.47
Krewski, 2005	USA	PM2.5 (most vs. least polluted city = 18.6 microg/m3 increase)	Lung Cancer Mortality	Age, sex, smoking, education, BMI, diabetes, occupational exposure to dust, gases or fumes	8,111	1.43	0.85-2.41
Laden, 2006	USA	PM2.5	Lung Cancer mortality	Age, sex, smoking, education, and BMI	8,096	1.27	0.96-1.69
			EUROPEAN STUDIES				
Cohort of Oslo men							
Nafstad, 2003	Norway	NO(x) (per 10 μg/m3 - home address)	Lung Cancer incidence	Age, smoking habits, and length of education	16,209	1.08	1.02-1.15
		SO_2 (per 10 μg/m3)	Lung Cancer incidence	Age, smoking habits, and length of education		1.01	0.94-1.08
French PAARC Study							
Filleul, 2005	France	Total Suspended Particulate (exceedance frequency of 200 μg/m3)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education	14,284	0.97	0.94-1.01
		Black Smoke (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.93-1.01
		NO (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.94-1.01
		NO_2 (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.97	0.85-1.10
		SO_2 (for 10 $\mu g/m^3$)	Lung Cancer Mortality	Age, sex, BMI, smoking, occupational exposure, education		0.99	0.92-1.07
GENAIR Cohort Study							
Vineis, 2006	Ten European Countries	PM10 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment,	197 cases	0.91	0.70-1.18

				country, occupational index and cotinine	556 controls		
		NO_2 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.14	0.78-1.67
		SO_2 (10 microg/m3 increase)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.08	0.89-1.30
		Proximity of residence to major road (exposed vs. nonexposed)	Lung Cancer Incidence	Age, BMI, education, gender, smoking, alcohol use, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index and cotinine		1.31	0.82-2.09
Netherlands Cohort Study on Diet and Cancer							
Beelen, 2008	Netherlands	Black smoke concentration	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status	40,114	1.47	1.01-2.16
		Traffic intensity on nearest road	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status		1.11	0.88-1.41
		Living near a major road	Lung Cancer incidence	Age, sex, smoking status, area-level socioeconomic status		1.55	0.98-2.43
Brunekreef, 2009	Netherlands	Black smoke (per 10 μg/m3)	Lung Cancer Mortality	Age, sex, smoking status, area-level socioeconomic status	120,000	1.03	0.88-1.20
		Traffic intensity (increase of 10,000 motor vehicles/day)	Lung Cancer Mortality	Age, sex, smoking status, area-level socioeconomic status		1.07	0.96-1.19
		Black smoke (per 10 μg/m3)	Lung Cancer Incidence	Age, sex, smoking status, area-level socioeconomic status		1.47	1.01-2.16
Diet, Cancer and Health cohort study							
Raaschou-Nielsen, 2011	Denmark	**NO_x** at **residence** (per 100 μg/m3 increase)	Lung Cancer Incidence	Age, smoking, ETS, length of school attendance, fruit intake, and employment	52,970	1.09	0.79-1.51
		Traffic load at residence (per 10^4 vehicle km/day)	Lung Cancer Incidence	Age, smoking, ETS, length of school attendance, fruit intake, and employment	52,970	1.03	0.90-1.19
Three Prospective Cohorts							
Raaschou-Nielsen, 2010	Denmark	$NOx^{\int}$ (30-72 μg/m3 vs. <30 μg/m3)	Lung Cancer Incidence	Smoking (status, duration, and intensity), educational level, body mass index, and alcohol consumption.	679 cases 3481 controls	1.30	1.07-1.57
		NOx (>72 μg/m3 vs. <30 μg/m3)	Lung Cancer Incidence	Smoking (status, duration, and intensity), educational level, body mass index, and alcohol consumption.		1.45	1.12-1.88

OTHER STUDIES							
Pope, 1995	USA	Most vs. Least polluted: Sulphates	Lung Cancer mortality	Smoking	552,138	1.15	1.09-1.22
		Most vs. Least polluted: Fine particles	Lung Cancer mortality	Smoking		1.17	1.09-1.26
Yorifuji, 2010	Japan	NO_2 (10 microg/m3 increase)	Lung Cancer mortality - non smokers	Smoking	14,001	1.3	0.85-1.93
Katanoda, 2011	Japan	PM2.5 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.24	1.12-1.37
		NO2 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.26	1.07-1.48
		SO2 (10 microg/m3 increase)	Lung Cancer mortality	Sex, age, smoking status, pack-years, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	63,520	1.17	1.10-1.26
Hales, 2011	New Zealand	PM10(1microg/m3 increase)	Lung Cancer mortality	Age, sex, ethnicity	1 050 222	1.015	0.004-1.026

Table 2 – Results on the association between air pollution and 1-OHP in the urine of exposed individuals: linear regression, logistic regression, and correlation analyses.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 541)	Subject desription	P
Castaño-Vinyals, 2004	Review	B[a]P	Not applicable	r: 0.76	17	Pairs of data - log transformed means - from different studies	0.038
Hansen, 2004	Copenhagen, Denmark	B[a]P†		r: 0.83		personal sampling of B(a)P: mean values	0.04
		Environmental pollution	Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	OR†: 1.51 (male) / 1.38 (female)	60 88	bus drivers mail carriers	0.08
Hansen, 2005	Denmark	Residence in urban vs. rural areas	Gender, time spent outside	OR: 1.29	102 100	children in Copenhagen children from rural residences	0.03
		One additional hour spent outside/day	Gender, residence	OR: 1.58	102 100	children in Copenhagen children from rural residences	<0.001
Freire, 2009	Granada, Spain	NO2 (predicted)	Exposure to ETS† and cooking appliance	β: 0.401	93 81	children with predicted exposure to NO2≥22.50 $\mu g,m^{-3}$ / children with predicted exposure to NO2<22.50 $\mu g,m^{-3}$	0.006
Hu, 2011	Taiwan	Residence near a coal fired power plant (PAH in air)	Age, gender, ETS, dietary exposure, and traffic	OR: 1.85 95%CI(1.43, 2.40)	146	Children in high exposure community 1 vs, Low exposure community 1	
				OR: 1.65 95%CI(1.30, 2.09)	88	Children in high exposure community 2 vs, Low exposure community 1	NA

≠ r = correlation coefficient; β = =linear regression coefficient (change in 1-OHP levels (7icromole/mol) for every unit change in exposure); OR = logistic regression odds ratio
† B[a]P Benzo [a] Pyrene; OR odds ratio; ETS environmental tobacco smoke.

Table 3 – Results on the association between air pollution and 1-OHP in the urine of exposed individuals: comparison of means analysis.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 742)	Mean (micromol/mol) ± SD (unless otherwise stated)	P
Ruchirawa, 2002	Bangkok, Thailand	Environmental air pollution	Smoking	Traffic policemen 41 Office policemen 40	0.181±0.078 0.173±0.151	 0.044
Hansen, 2004	Copenhagen, Denmark	Environmental pollution	Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	Bus drivers – all 117samples Mail Carriers – all 93samples	0.19 (Range: 0.05-1.60) 0.11 (Range: 0.02-0.75)	 <0.001
			Job, gender, NAT2 phenotype, age, vehicle exhaust, cooked food mutagens, physical exercise	Mail carriers Working outdoors 56samples Mail Carriers Working indoors 37samples	0.14 (Range: 0.02-0.75) 0.08 (Range: 0.02-0.57)	 <0.001
Tuntawiroon, 2007	Bangkok and Chonburi, Thailand	PAH† from traffic related sources	Age and lifestyle (i.e. ETS†,diet, transportation, medication etc.)	Bangkok schoolchildren 115 Group matched provincial school children – Day 0 69	0.18±0.01 0.1±0.01	 <0.0001
				Bangkok schoolchildren Day 1 115 Group matched provincial school children – Day 1 69	0.22±0.02 0.12±0.01	 <0.0001
Freire, 2009	Granada, Spain	Residence in urban vs. rural areas	Exposure to ETS† and cooking appliance	4yr old children living in urban 118 4yr old children living in rural areas 56	0.060 ± 0.040 0.054 ± 0.055	 0.20
Martinez-Salinas, 2010	Mexico	Traffic related air pollution	NA	Children in area with low vehicular traffic 39 Children in area with high vehicular traffic 17 Children in all communities of the study 258	0.8 ± 0.2 0.2 ± 0.2	<0.05 >0.05 *P-values compared to children from all communities
Hu, 2011	Taiwan	Residence near a coal fired power plant (PAH in air)	NA	High Exposure Community -1 146 High Exposure Community -2 88 Low Exposure Community -1 86 Low Exposure Community -2 49	0.186 ± 0.148 0.194 ± 0.143 0.113 ± 0.082 0.122 ±0.089	 NA

† PAH polycyclic aromatic hydrocarbons; ETS environmental tobacco smoke.

Table 4 – Results on the association between air pollution and DNA adducts in exposed individuals; linear regression, logistic regression and correlation analyses

First author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 1787)	Subject desription	P
Binkova, 1995	Czech Republic	Outdoor air pollution – individual PAH†	Age, active and passive smoking, consumption of fried or smoked food, job category	r: 0.541	21	Non smoking women working outdoors up to 8 hours – gardeners or postal workers	0.016
Whyatt, 1998	Krakow, Poland	Ambient pollution at mother's place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH & other organics	β: 1.77	19	mothers not employed away from home	0.05
		Ambient pollution at place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH and other organics.	β: 1.73	23	newborns of mothers (high pollution / low pollution group)	0.03
Sørensen, 2003	Copenhagen	Personal PM2.5	Smoking, diet, season	ß=-0.0035	75	Students monitored 4 seasons of a year	0.31
Castaño-Vinyals, 2004	Review	B[a]P† (stationary meas.)	Not applicable	r: 0.6	12	pairs of data	0.038
Peluso, 2005	10 European countries	O_3† levels	Age, gender, educational level, country and batch	β: 0.066	564	EPIC cohort subjects	0.0095
Neri, 2006	Review	Environmental pollutants (including ETS† exposure)	Not applicable	Not applicable	178	Newborns – 17yr olds 2 studies in total – 2 with statistically significant results	Not applicable
Pavanello, 2006	North-East Italy	B[a]P indoor exposure	Smoking, diet, area of residence, traffic near house, outdoor exposure	β: 0.973	457	municipal workers (non smoking)	0.012
Palli, 2008	Florence City, Italy	PM10† (from high traffic stations)	Smoking	r: 0.562	16	traffic exposed workers	0.02
Peluso, 2008	Thailand	Industrial estate residence	Smoking habits, age, gender	OR†: 1.65	72 50	Industrial estate residents control district residents	<0.05
			Smoking habits, age, gender	OR: 1.44	64 72	PAH exposed workers industrial estate residents	<0.05
Pavanello, 2009	Poland	1-pyrenol	NA†	r: 0.67	92	coke oven workers and controls	<0.0001
Pedersen, 2009	Copenhagen, Denmark	Residential traffic density	ETS†, use of open fireplace, pre-pregnancy weight, folate levels, vitamin B12 levels, maternal education and season of delivery	β: 0.6 / 0.7	75 /69	Women /umbilical cords	<0.01
Garcia-Suastegui, 2011	Mexico City, Mexico	PM2.5	Various risk alleles	r: NR	92	Young adults living in Mexico City	0.013
		PM10	Various risk alleles	r: NR	92	Young adults living in Mexico City	0.035
Herbstman, 2012	USA	PAH exposure – measured in both air and urine	NA	r: NR	NR	152 participants – prenatal exposure, DNA adducts in cord blood	Not significant

≠ r = correlation coefficient; β =linear regression coefficient (change in DNA adduct levels (adducts/10^8 nucleotides) for every unit change in exposure); OR = logistic regression odds ratio
† PAH polycyclic aromatic hydrocarbons, PM10 particulate matter of diameter less than 10 microns; B[a]P Benzo [a] Pyrene; O_3 ozone; NA not available; ETS environmental tobacco smoke; OR odds ratio

Table 5 – Results on the association between air pollution and DNA adducts in exposed individuals; comparison of means analysis.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 1044)	Mean adducts/ 10^8 nucleotides ± SD (unless otherwise stated)	P
Perera, 1991	Poland	Environmental air pollution	NA†	Residents in industrial area 20	30.4±13.5	
				Rural controls 21	11.01±22.6	<0.05
Hemminki, 1994	Stockholm, Sweeden	Traffic related air pollution	Age, smoking	Bus drivers – urban routes 26	0.9 ± 0.35	Non sig.
				Bus drivers – sub urban routes 23	1.4 ± 0.48	<0.001
				Taxi drivers – mixed routes 19	1.6 ± 0.91	<0.010
				Controls 22	1.0 ± 0.32	
Nielsen, 1996	Denmark	Environmental air pollution	Smoking, PAH† rich diet	Bus drivers in Central Copenhagen 49	Median: 1.214 Range: 0.142-22.24	
				Rural controls 60	Median: 0.074 Range: 0.003-8.876	0.001
Nielsen, 1996 (2)	Denmark and Greece	Environmental air pollution	Smoking, sex	Students in urban universities 74	Median: 0.205	
				Students in agricultural colleges 29	Median: 0.152	0.02
Yang 1996	Milan, Italy	Traffic related air pollution	Sex, age, smoking habits	News stand workers at high traffic areas 31	2.2 ± 1.0	
				News stand workers at low traffic areas 22	2.2 ± 1.2	0.27
Topinka, 1997	Teplice & Prachatice, N&S Bohemia	Residence in Industrial area	NA†	Placenta samples- industrial polluted area (winter): GSTM− genotype 15	1.49 ± 0.70	
				Placenta samples –agricultural area (winter): GSTM− genotype 17	0.96 ± 0.55	0.027
Merlo, 1997	Genova, Italy	Ambient PAH concentrations	NA†	Traffic police workers 94	1.48 ± 1.35	
				Urban residents 52	1.01 ± 0.63	0.007
Ruchirawa, 2002	Bangkok, Thailand	Environmental air pollution	Smoking, sex	Traffic Policemen 41	1.6±0.9	
				Office duty policemen 40	1.2±1.0	0.03
Marczynski, 2005	Germany	PAH in air (ambient and personal monitoring)	NA†	Samples from 16 workers(increased PAH exposure)	Range: 0.5 – 1.19Range: <0.5 –	
				Samples from 16 workers¥ (reduced PAH exposure)	0.09	<0.0001
Topinka, 2007	Prague, Czech Republic	c-PAH† (personal exposure)	Smoking, ocuupational duration	109 policemen – January (highest exposure)	2.08±1.60	
				109 policemen – March	1.66±0.65	<0.0001
Tuntawiroon, 2007	Bangkok and Chonburi, Thailand	c-PAH and B[a]P†	Age and lifestyle (i.e. ETS†, transportation, medication, diet etc.)	Bangkok schoolchildren 115	0.45±0.03	
				Provincial school children (group matching) 69	0.09±0.00	<0.0001
Fanou, 2011	Cotonou, Benin	Environmental air pollution	NA†	Taxi-motorbike drivers 13	24.6±6.4	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Street food vendors 16	34.7±9.8	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Gasoline salesmen 20	37.2±8.1	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	
		Environmental air pollution	NA†	Street side residents 11	23.78±6.9	<0.001
				Intermediate exposure suburban group 20	2.1±0.6	

† N/A not applicable; NA not available; PAH polycyclic aromatic hydrocarbons; c-PAH carcinogenic polycyclic aromatic hydrocarbons; B[a]P benzo [a] pyrene; ETS environmental tobacco smoke
¥ The sample sizes reported in the summary tables refer to subjects with measurments available both before and after change in work conditions

Table 6 - Results on the association between air pollution and oxidatively damaged nucleobases/deoxynucleosides in urine or mononuclear blood cells; comparison of means analysis

First author, Year	Area, country	Exposure definition/source Referents' definition	Biomarker	Groups Sample size (Total: 2827)	Level (Mean ± SD, unless otherwise stated)	Controlled confounders
Suzuki 1995	Japan	Sampling before and after a stay in a street	8-oxoGua in urine (HPLC-ECD)	3	After:9.9±2.5 Before: 4.22±2.0 (pooled data from several timepoints 0-24 after exp.)	Cross-over study
Calderon-Garciduenas 1999	Mexico	Children in urban and low-polluted area	8-oxodG in nasal epithelial cells (immunohistochemistry)	Exposed: 86 Controls: 12	602 ± 195* 210 ±122	NA†
Autrup 1999; Loft 1999	Copenhagen, Denmark	Bus drivers in the city center and rural/suburban controls	8-oxodG in urine (HPLC-ECD)	Exposed: 29 Controls:20	1.74 ± 4,69 1.54 ± 4.29	Age, BMI†, metabolic and DNA repair phenotype
Staessen 2001	Belgium	Adolescents from industrial and rural areas	8-oxodG in urine (HPLC-ECD)	Peer: 100 Wilrijk: 42 Hoboken: 58	0.44 (0.40-0.48) 0.57 (0.49-0.66)* 0.49 (0.42-0.56) Geometric mean and 95% CI	Sex, smoking
Chuang 2003	Taiwan	Taxi-drivers and controls	8-oxodG in urine (ELISA)†	Exposed: 95 Controls: 75	0.33± 0.20* 0.20 ± 0.14	Age, education, exercise
Lai 2005	Taipei city, Taiwan	Highway toll station workers and controls	8-oxodG in urine (ELISA)	Exposed: 47 Controls: 24	13.3±7.1* 8.4±6.2	Age, smoking
Harri 2005	Finland	Garage/waste workers and controls	8-oxodG in urine and MNBC (HPLC-ECD)	**Urine:** Exposed: 29 Controls: 36 **MNBC:** Exposed: 19 Controls: 18	Winter: 1.52 ± 0.44 1.56 ± 0.61 Summer: 1.61±0.33 1.43±0.4 4.84± 0.17 4.11 ±0.16	Age, smoking, BMI
Vinzents 2005	Copenhagen, Denmark	Sampling after cycling in traffic-intense streets or laboratory	FPG sites in MNBC	15	Traffic: 0.08 (0-0.04)* Lab: 0.02 (0-0.04)	Cross-over study
Avogbe 2005	Rep. of Benin	Subjects from urban and rural areas	FPG sites in MNBC	Taximoto: 24 Roadside: 37 Suburban: 42 Rural: 27	1620 ± 310* 1250 ± 198* 1110 ± 188* 650 ± 160	Metabolic genes
Fanou 2006	Rep. of Benin	Taxi-moto drivers and controls	8-oxodG in MNBC (HPLC-ECD)	Exposed: 35 Controls: 6	2.05±1.25* 1.11±0.82	NA†
Cavallo 2006	Italy	Airport personnel and controls	FPG sites in MNBC	Exposed: 41 Controls: 31	55.86 ± 12.85* 43.01 ± 7.97	Age, smoking, dietary habits
Bräuner 2007	Copenhagen, Denmark	Sampling before and after controlled exposure to street PM	FPG sites in MNBC	29	Air: 0.53 (0.37-0.65)* FA†:0.38 (0.31-0.53) Median and quartiles	Age, sex, smoking, CVD†, BMI
Singh 2007	Prague (Czech Rep.) Kosice (Slovakia) Sofia (Bulgaria)	City policemen, bus drivers and controls	8-oxodG (LC-MS/MS) M_1dG (immunoslot blot) In MNBC	Exposed: 98 Controls: 105 Exposed: 198 Controls: 156	33.0±30.1 29.2±21.2 58.3±37.5 49.2±30.3	Smoking, demographic variables, diet
Novotna 2007	Prague, Czech Rep.	Policemen and controls sampled in different seasons	ENDOIII/FPG sites in MNBC	Exposed: 54 Controls: 11	Jan: 2.91± 1.84* Sep: 2.12 ± 1.62 Jan:1.36± 1.53 Sep: 1.22 ± 0.96	Metabolic and DNA repair genotypes
Rossner, Jr. 2007,	Prague, Czech Rep.	Bus drivers and controls sampled in	8-oxodG in urine	Exposed: 50	7.59 ± 2.25*	Medical history, lifestyle

2008		there different seasons	(ELISA)		6.73 ± 2.48* 5.67 ± 2.50*	
				Controls: 50	6.29 ± 2.59 5.51 ± 2.36 3.82 ± 1.73	
Buthbumrung 2008	Thailand	Schoolchildren in Bangkok and rural controls	8-oxodG in leukocytes and urine (HPLC-ECD)	Exposed: 40 Controls: 32	0.25 ± 0.13 0.08 ± 0.34	Metabolic genes
				Exposed 43 Controls: 32	2.16 ± 1.84 1.32 ±1.24	
Danielsen 2008	Sweden	Sampling before and after controlled exposure to wood smoke	8-oxodG 8-oxoGua in urine: HPLC-GC/MS FPG sites in MNBC	13	16.4% (95% CI: -6.9,45.5) 79.3% (95% CI -12.9,269) -15% (95% CI:-31.1,4.9)	Cross-over study
Palli 2009	Florence, Italy	Metropolitan area	FPG sites in MNBC	Exposed 44 Controls: 27	5.0 ± 3.06 4.11 ± 3.96	Sex, smoking, season
Svecova 2009	Teplice and Prachatice (Czech Rep.)	Children	8-oxodG in urine (ELISA)	Teplice: 495 Prachatice:399	14.6 (3.1-326.5) 15.2 (3.0-180.8)	Ethinicity, mothers smoking, education, sex, age, atopic diseases
Bagryantseva 2010	Praque, Czech Rep.	Bus drivers, garage men and office workers	8-oxodG in urine (ELISA)	Bus drivers: 50 Garage men: 20 Controls: 50	5.67 ± 2.5* 6.54 ± 6.9* 3.82 ± 1.73	Age, vitamins, plasma lipids, metabolic and DNA repair genes
			EndoIII/Fpg sites in lymphocytes	Bus drivers: 50 Garage men: 20 Controls: 50	2.35 ± 2.17 2.56 ± 2.52 2.55 ±2.86	
Han 2010	Taiwan	Bus drivers and office workers	8-oxodG in urine (ELISA)	Exposed: 120 Controls: 58	9.5 ± 5.7* 7.3 ± 5.4	Age, BMI, smoking. Alcohol, areca chewing, tea, coffee energy drink, exercise
Fan 2011	GuangZhou City, China	Children	8-oxodG in urine (ELISA)	Exposed: 39 Controls: 35	20.87 ± 14.42 16.78 ± 13.30	Age, sex, height, weight, passive smoking, diet, transportation tool and time taken to/from school
Rossner, Jr, 2011	Praque and Ostrava (Czech Rep.)	Policemen and office workers	8-oxodG in urine (ELISA)	Ostrava: 75 Praque: 65	4.28 ± 2.27 4.84 ± 1.61	Age, passive smoking, cotinine, plasma lipids, vitamins, DNA repair gens

† BMI body mass index; NA not available; CVD cardiovascular disease; ELISA enzyme-linked immunosorbent assay**;** FA filtered air

Table 6a. Confounding in studies of DNA adducts

Adjustment	Number of studies	References
Several relevant confounders including smoking but not diet	**7**	**Hemminki 1994, Nielsen 1996, Peluso 2005, Peluso 2008, Ruchirawa 2002, Topinka 2007, Yang 1996,**
Several relevant confounders including smoking including diet	**7**	**Binkova 1995, Nielsen 1996 (2), Pavanello 2006, Pedersen 2009, Sorensen 2003, Tuntawiroon 2007, Whyatt 1998,**
Smoking	**1**	**Palli 2008**
Various Risk Alleles	**1**	**Garcia-Suastegui 2011**
Confounding not relevant	**1**	**Marczynski 2005**
No information about confounding factors	**6**	**Ayi Fanou 2011, Herbstman 2012, Merlo 1997, Pavanello 2009, Perera 1991, Topinka 1997**

Table 7 - Results on the association between air pollution and oxidatively damaged nucleobases/deoxynucleosides in urine or mononuclear blood cells; linear regression and correlation analysis

First author, year	Area, country	Exposure definition/source	Biomarkers and methods	Sample size (Total: 1642)	Effect Measure≠	Controlled confounders
Lagorio 1994	Rome Italy	Filling station attendants	8-oxodG in urine (HPLC-ECD)	65	r = 0.34* (benzene)	Age, length of employment, smoking, exposure to X-ray
Sørensen 2003a	Copenhagen, Denmark	Students living in the metropolitan area	8-oxodG (HPLC-ECD) in urine and MNBC		β = 0.010* (8-oxodG, lymphocytes) β = -0.007 (8-oxodG, urine)	Season, sex, outdoor temperature
			FPG/EndoIII sites in MNBC	50	β = 0.0025 (EndoIII) β = 0.014 (FPG)	
Sørensen 2003b	Copenhagen, Denmark	Healthy subjects living in the metropolitan area	FPG/EndoIII sites in MNBC 8-oxodG (HPLC-ECD) in urine and MNBC	40	r_s = 0.39* Non-significant	Smoking, type of work, sex, genotype (metabolism)
Vinzents 2005	Copenhagen, Denmark	Sampling after cycling in traffic-intense streets or laboratory	FPG sites in MNBC	15	$\beta=1.5x10^{-3}$ per ultrafine particle time weighted exposure unit	Cross-over study
Bräuner 2007	Copenhagen, Denmark	Sampling before and after controlled exposure to street PM	FPG sites in MNBC	29	NC_{12}†: β = -0.033 NC_{23}: β =0.066* NC_{57}: β=0.040*	Age, sex, smoking, CVD†, BMI† included in model
Chuang 2007	Taipei, Taiwan	College students living in the metropolitan area	8-oxodG in plasma (ELISA)	76	PM10: -9.2%, (95% CI: -21.5;3.2) PM2.5: -5.0% (95% CI: -14.3-4.4) O3: 2.2% (95% CI: 0.9;3.5)	Sex, age, BMI, weekday, temperature, relative humidity
De Coster 2008	Flanders, Belgium	Industrial and urban areas	8-oxodG in urine (ELISA)	399	β = 0.179 (95% CI: 0.077-0.282) with 1-OHP as biomarker of internal exposure	Age, Sex, recent smoking
Svecova 2009	Teplice&Prachatice (Czech Rep.)	Children living in the two areas	8-oxodG in urine (ELISA)	Teplice: 495 Prachatice:399	β=0.16* (air pollutants)	Ethinicity, mothers smoking, education, sex, age, atopic diseases
Allen 2009	Washington, USA	Subjects with MetS with controlled exposure to diesel exhaust	8-oxodG in urine (ELISA) †	10	β = 0.087 (95% CI: -0.13; 0.31)	Cross-over study
Kim 2009	Boston, USA	Subjects with hypertension and controls (panel study)	8-oxodG in urine (ELISA)	21	β=-0.60 (hypertensive) β=1.1 (controls)	Age, sex, smoking, time of the day
Bagryantseva 2010	Praque, Czech Rep.	Bus drivers, garage men and office workers	8-oxodG in urine (ELISA)	120	β= 0.105 /BaP β= 0.026 (PAH)	Age, vitamins, plasma lipids, metabolic and DNA repair genes
			EndoIII/FPG sites in lymphocytes	120	β=-0.62 (BaP) β=-0-056 (PAH)	
Lee 2010	Taiwan	Inspection station workers and controls	8-oxodG in urine (ELISA)	Exposed:11 Controls: 32	β=7.47 (SE = 3.3)*	Smoking, cooking at home
Fan 2011	GuangZhou City, China	Children in a kindergarten	8-oxodG in urine (ELISA)	74	r=0.055 (OH-PAH)	Age, sex, height, weight, passive smoking, diet, transportation to/from kindergarten
Mori 2011	Tokyo	Children in a kindergarten	8-oxodG in urine (ELISA)	76	β=0.216 (Ln(1-OHP))	Age, sex, Mn, As, vitamin A, vitamin C, cotinine
Ren 2011	Boston, USA	Eldery subjects	8-oxodG in urine (ELISA)	320	PM2.5: 30.8% (95% CI: 9.3-52.2)	Age, BMI, smoking, vitamins
Rossner, Jr 2011	Praque, Czech Rep.	Policemen	8-oxodG in urine (ELISA)	59	β= 0.04* (PM2.5 stationary monitoring station) β=0.16 (BaP) β=-0.02 (PAH)	Age, cotinine, cholesterol, triglycerides

≠ r = correlation coefficient; β = linear regression coefficient (change in levels of oxidatively damaged nucleobases for every unit change in exposure); % per cent difference
† MetS metabolic syndrome; ELISA enzyme-linked immunosorbent assay; BMI body mass index; CVD cardiovascular disease, $NC_{size\ cut\ off}$ Number concentration.

Table 7a. Confounding in studies of oxidative damaged to nucleobases in blood or urine

Adjustment	Number of studies	References
Several relevant confounders including smoking	**23**	**Autrup 1999, Brauner 2007, Cavallo 2006, Chuang 2003, Chuang 2007, De Coster 2008, Fan 2011, Han 2011, Harri 2005, Kim 2009, Lagorio 1994, Lai 2005, Lee 2010, Loft 1999, Palli 2009, Ren 2011, Rossner 2007, Singh 2007, Sorensen 2003a, Sorensen 2003b, Staessen 2001, Svecova 2008, Svecova 2009**
Metabolic and/or DNA repair gene polymorphisms	**5**	**Avogbe 2005, Bagryantseva2010, Buthbumrung 2008, Novotna 2007, Rossner 2011**
Confounding not relevant	**4**	**Allen 2009, Danielsen 2008, Suzuki 1995, Vinzents 2005,**
No information about confounding factors	**2**	**Ayi Fanou 2006, Calderón-Garcidueñas 1999,**

Table 8 – Results on the association between air pollution and CAs in the cells of exposed individuals; logistic regression and comparison of means analyses.

First author, Year	Area/ Country	Exposure	Controlled Confounders	Groups Sample Size (Total: 1265)	Mean (% frequenciesΔ) ± SD	P
Knudsen, 1999	Copenhagen, Denmark	Air pollution (urban)	Metabolic genotypes, DNA repair, age, sex	office workers 41	2.46 ± 1.98	
				postal workers 60	2.12 ± 1.38	Not significant
				Bus drivers – high exposure 55	2.84 ± 1.87	
				Bus drivers – low + medium exposure 45	2.24 ± 1.57	Not significant
Sram 1999	Czech Republic	Urban air pollution	Maternal height and pre-pregnancy weight, parity, marital status, education and maternal smoking, season and the year of the study	Pregnant Mothers: Industrial + residential heating (Teplice) 131	1.54 ± NA†	
				Pregnant Mothers: Residents in agricultural districts (Prachatice) 48	1.04 ± NA†	<0.05
Kyrtopoulos, 2001	Athens and Halkida, Greece	Air pollution (in city of studying)	Smoking	Students in Athens (higher PAH† exposure & lower PM2.5† exposure) 222	0.88±0.97	
				Students in Halkida (lower PAH exposure & higher PM2.5 exposure) 149	1.06±1.12	Not significant
Burgaz, 2002	Ankara, Turkey	Air pollution (traffic related)	Age, sex, smoking habits	Traffic policemen 18	1.29±0.30	
				Control group 5	0.26±0.14	<0.05
				Taxi drivers 29	1.82±0.34	
				Control group 5	0.26±0.14	<0.01
Sram, 2007	Prague, Czech Republic	c-PAHs† on respirable air particles (<2.5 m)	Smoking, medical histories	Sampling in January: higher PM† and PAH exposures 61	0.27±0.18	
				Sampling in March: lower PM and PAH exposures 61	0.16±0.17	<0.001
Zidzik, 2007	Kosice (Slovakia), Prague(Cz.Republic) & Sofia (Bulgaria)	cPAH	Sex	Exposed policemen in Kosice 51	2.6±2.64	
				Controls in Kosice 55	2.14± 1.61	Not significant
				Exposed policemen in Prague 52	2.33±1.53	
				Controls in Prague 50	1.94±1.28	Not significant
				Exposed policemen in Sofia 50	3.04±1.64	
				Controls in Sofia 45	1.79±0.77	<0.05
				Exposed bus drivers in Sofia 50	3.6±1.63	
				Controls in Sofia 45	1.79±0.77	<0.05
Balachandar, 2008	Tamilnadu, India	ETS†	Age	Group I : <6hrs exposure/day and <30yrs old		
				Passive smokers 18	5.00 ± 1.68,	
				Controls 18	1.16 ± 0.92,	Significant
				Group II : >6hrs exposure/day and >30yrs old		
				Passive smokers 25	9.04 ± 3.73	
				Controls 25	2.76 ± 2.12.	Significant
Rossnerova, 2011	Prague and Ceske Budejovice, Czech Republic	Air pollution (urban vs. rural)	Sex	Mothers in Prague (urban) 86	0.80 ± 0.27	<0.001
				Mothers in Ceske Budejovice (rural) 92	0.61 ± 0.21	
					Linear Regression Coefficient (95% CI)	
Garcia-Suastegui, 2011	Mexico City, Mexico	Air pollution – PM10	Unadjusted	91 individuals sampled during dry season	NA	0.669
		Air pollution – PM2.5				0.399
		Air pollution – PM10	Unadjusted	80 individuals sampled during rainy season	NA	0.709
		Air pollution – PM2.5				0.843
					Logistic regression OR$^{\infty}$ (95% CI)	
Rossner, 2011	Prague and Ostrawa, Czech Republic	Air pollution at residence	Age, benzene exposure, cotinine plasma levels, total, HDL, and LDL cholesterol levels, triglycerides, Vitamins a, C and E in plasma and various gene expressions	Subjects in Prague (less polluted) 64		
				Subjects in Ostrawa (more polluted) 75	0.18 (0.05-0.67)$^{\infty}$	0.010

† NA not available; PAH polycyclic aromatic hydrocarbons; PM2.5 particulate matter with dimater less than 2.5 microns; N/A not applicable; c-PAH carcinogenic polycyclic aromatic hydrocarbons; ETS environmental tobacco smoke.

Δ Percentage of cells with chromosomal aberrations

$^{\infty}$ Odds ratio of having chromosomal aberrations above median, for subjects in Prague compared to subjects in Ostrawa

Table 9 – Results on the association between air pollution and MN in peripheral blood cells of exposed individuals: linear regression analyses

First Author, Year	Area/ Country	Exposure	Controlled Confounders	Effect Measure≠	Sample Size (Total: 1478)	Subject desription	p
Neri, 2006	Review	Environmental Pollutants	Not applicable		1071	Children: 1-16 yrs old 4 studies in total – 4 with statistically significant results	
Ishikawa, 2006	Shenyang city, China	Air pollution (ambient)	Smoking habits, sex, age, metabolic enzyme and DNA repair gene polymorphisms	β: 1.57	66 63	Female industrial Female rural residents	<0.05
Pedersen, 2009	Copenhagen, Denmark	Residential traffic density (validated by indoor levels of nitrogen dioxide and PAH)	ETS exposure, use of open fireplace, prepregnancy weight, folate levels, vitamin B12 levels, maternal education and season of delivery	β: -0.1 β: 0.4	75 69	Women Umbilical cords	0.02
				Mean (% frequencies) ± SD			
Merlo, 1997	Genova, Italy	Ambient PAH concentrations	Sex	3.73 ± 1.6 4.03 ± 1.61	82 52	Traffic police workers Urban residents	0.38
Rossnerova, 2011	Prague and Ceske Budejovice, Czech Republic	Air pollution (urban vs. rural)	Sex	8.35 ± 3.06 6.47 ± 2.35	86 92	Mothers in Prague (urban) Mothers in Ceske Budejovice (rural)	<0.001

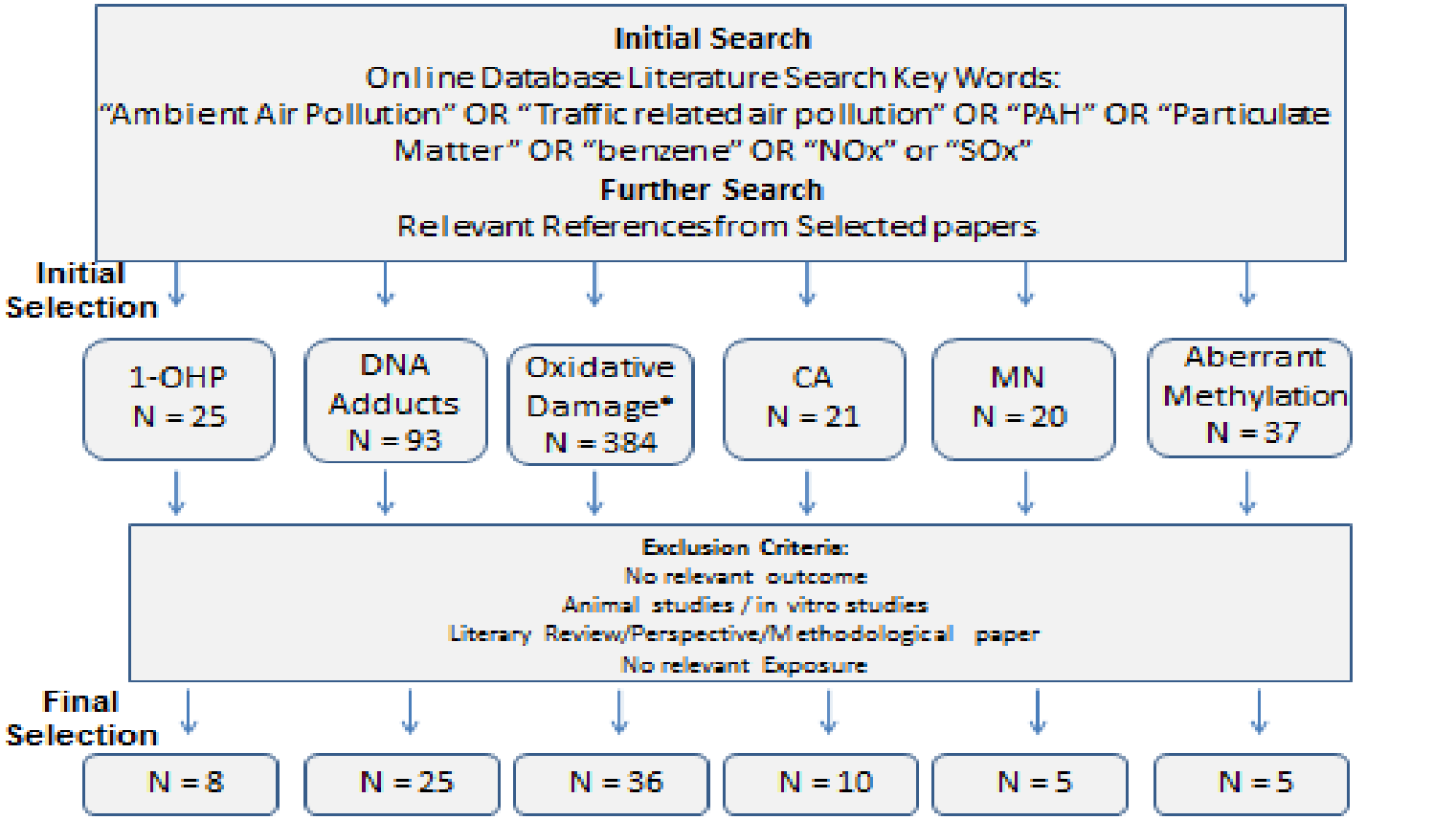
≠ β = linear regression coefficient (change in micronuclei frequencies (frequency per 1000 cells) per unit change in exposure)
† PBLs peripheral blood lymphocytes; N/A not applicable; PM10 particulate matter with dimater less than 10 microns; polycyclic aromatic hydrocarbons.

Table 10 - Results on the association between air pollution and methylation changes in the cells of exposed individuals.

First author, Year	Area/ Country	Exposure	Outcome	Controlled Confounders	Effect Measure≠	CI†	Sample Size (Total: 1499)	Subject desription	P
Baccarelli, 2007	Boston, USA	Ambient Black Carbon (hourly concentrations measured at a monitoring site approximately 1 km from the site of examination (7 day mean))	LINE-1 methylation	Multiple clinical and environmental covariates	r: -0.11	(-0.18) (-0.04)	718	subjects from the Normative Aging Study	0.002
		Ambient Black Carbon (hourly concentrations measured at a monitoring site approximately 1 km from the site of examination (7 day mean))	Alu methylation	Multiple clinical and environmental covariates					Not significant
Baccarelli, 2009	Boston, USA	PM2.5† concentrations (7day mean)	LINE-1 methylation	Age, BMI, cigarette smoking, pack-years, statin use, fasting blood glucose, diabetes mellitus, percent lymphocytes, and neutrophils in differential blood count, day of the week, season, and outdoor temperature	r: -0.13	(-0.19) (-0.06)	718	subjects from the Normative Aging Study	<0.001
		PM2.5 concentrations (7day mean)	Alu methylation	Age, BMI, cigarette smoking, pack-years, statin use, fasting blood glucose, diabetes mellitus, percent lymphocytes, and neutrophils in differential blood count, day of the week, season, and outdoor temperature	r: -0.01	(-0.07) (0.05)			0.71
Tarantini, 2009	Brescia, Northern Italy	PM10 (first day of the week and after 3 days of work)	LINE-1 methylation	Unadjusted	0.02%	SE: 0.11	63	workers	0.89
		PM10 (first day of the week and after 3 days of work)	Alu methylation	Unadjusted	0%	SE: 0.08			0.99
		PM10 (first day of the week and after 3 days of work)	iNOS promoter methylation	Unadjusted	-0.61%	SE: 0.26			0.02
		PM10 (average level of individual exposure)	LINE-1 methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.34	SE: 0.09			0.04
		PM10 (average level of individual exposure)	Alu methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.19	SE: 0.17			0.04
		PM10 (average level of individual exposure)	iNOS promoter methylation	Age, BMI, smoking, number of cigarettes/day	β: -0.55	SE: 0.58			0.34
Madrigano, 2011	New York, USA	PM2.5 (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	0.03%	(-0.12) (0.18)	706	subjects from the Normative Aging Study	Not Significant
			Alu		0.03%	(-0.07) (0.13)			Not Significant
		Black Carbon (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	-0.21%	(-0.50) (0.09)			Not Significant
			Alu		-0.31%	(-0.12) (-0.50)			P<0.05
		SO4 (IQR increase over a 90 day period)	LINE1	Season, time, smoking, BMI, alcohol intake, medication, batch, % WBC type	-0.27%	(-0.02) (-0.52)			P<0.05
			Alu		-0.03%	(-0.20) (0.13)			Not Significant
Herbstman, 2012	New York, USA	PAH exposure – prenatal	Global Methylation	Ethnicity	β: -0.11	(-0.21) (0.00)	164	cord blood samples	0.05

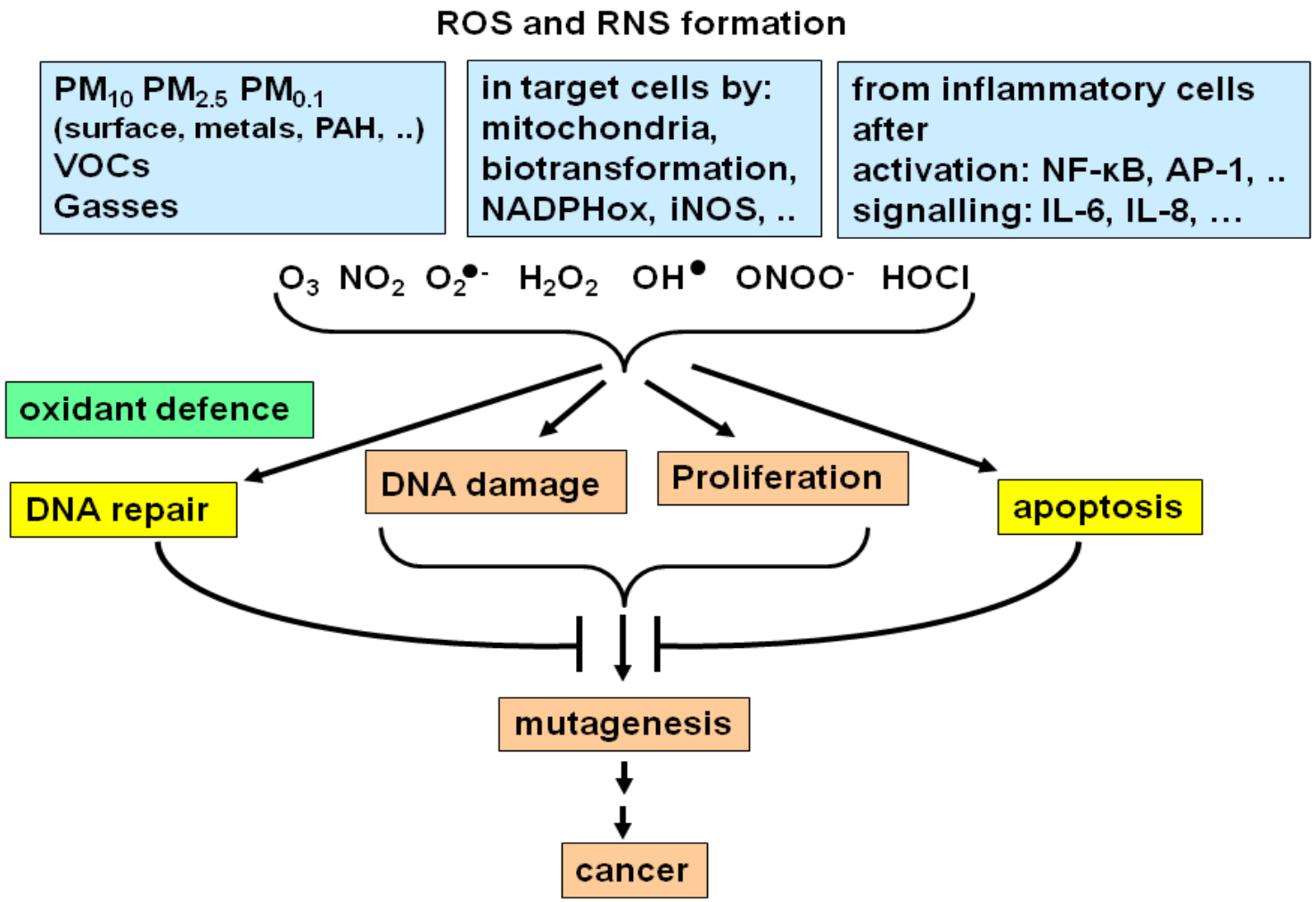
≠ r = correlation coefficient; β = linear regression coefficient (change in DNA methylation levels (**%5mC)** per unit change in exposure); % per cent difference
† CI confidence interval; LINE-1long interspersed nuclear element-1; PM10 particulate matter with diameter of less than 10 microns; tHcy total homocysteine; BMI body mass index; PM2.5 particulate matter with diameter of less than 2.5 microns; PAH polycyclic aromatic hydrocarbons.

Figure 1 - Flow Chart of Literature Review



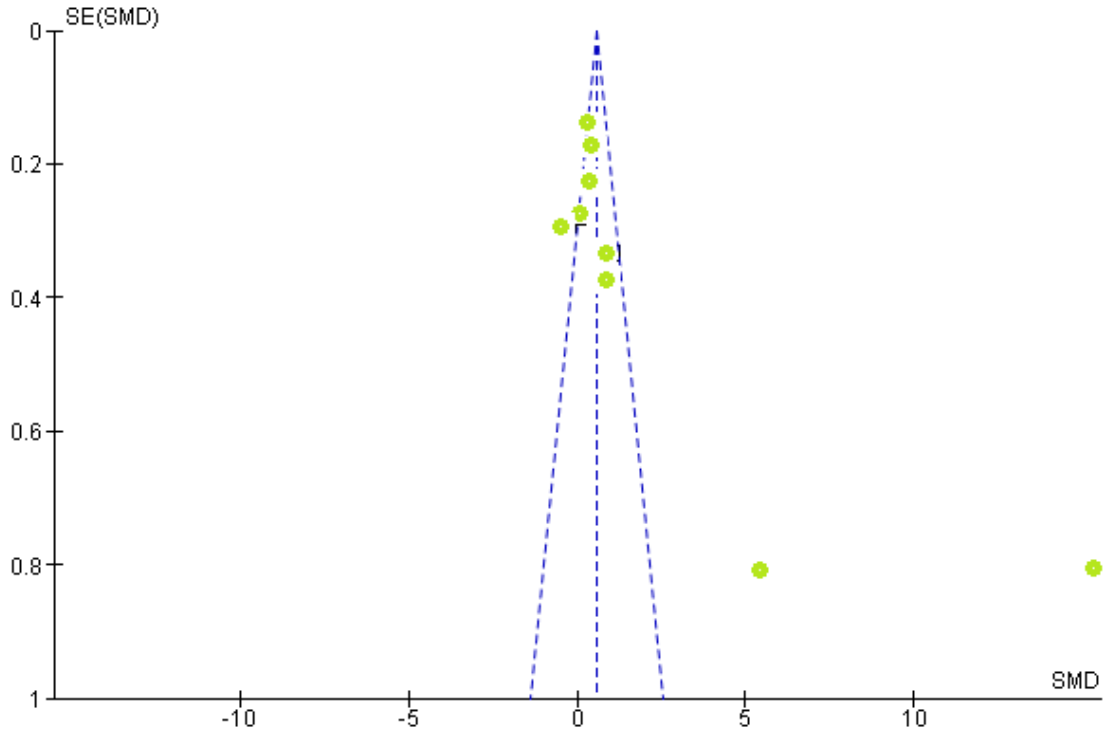
* For oxidative damage search terms also included: "diesel exhaust", "wood smoke", and "biomass".

Figure 2 – Putative Mechanisms of cancer through oxidative damage from air pollution



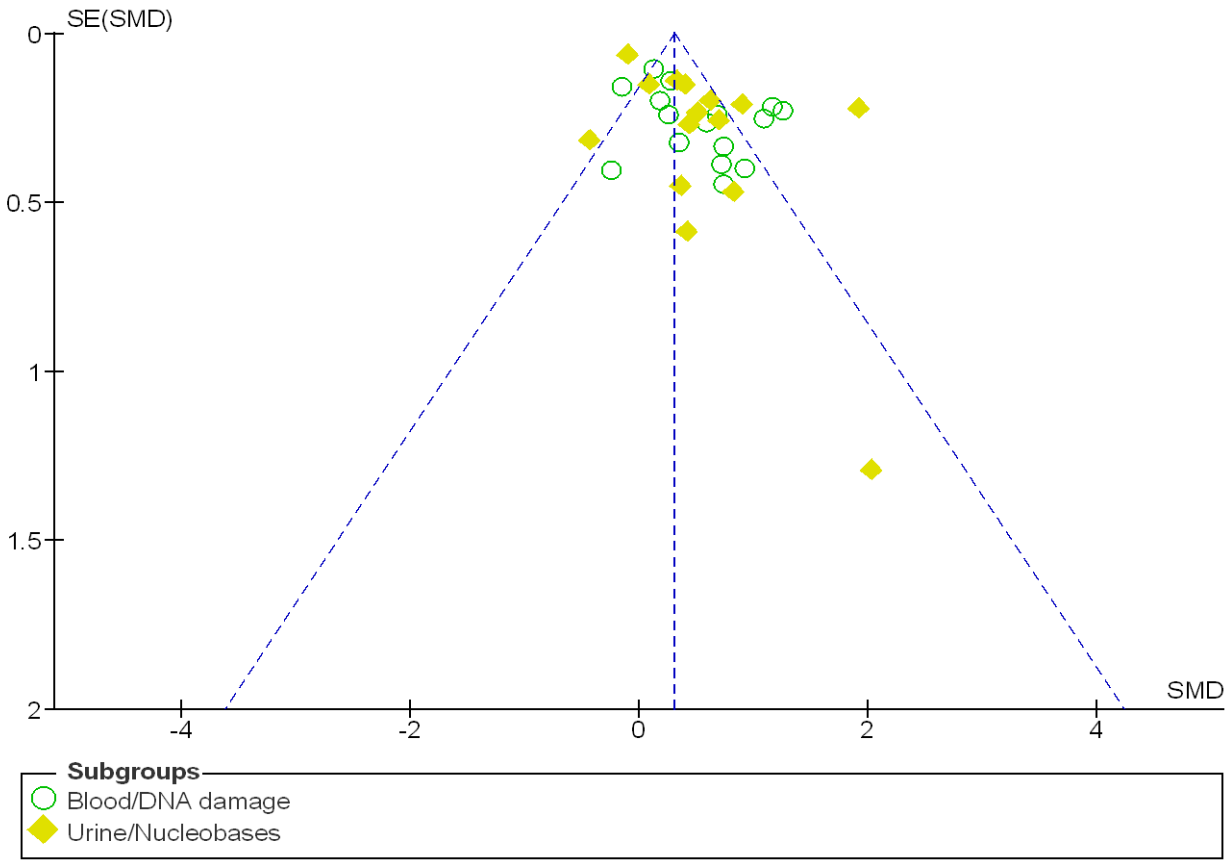
Adapted from: Risom, L, P. Møller, and S. Loft (2005) Oxidative stress-induced DNA damage by air pollution, Mutat. Res. 592:119-137

Figure 3 - Funnel plot of the standard error of the standardized mean difference (SMD) vs the SMD of studies on DNA adducts (in a fixed effects model to get the pseudo CI lines).



NOTE: Three studies not reporting means and standard deviations were excluded (Nielsen 1996a, Nielsen 1996b, Marczynski 2005).

Figure 4 - Funnel plot of the standard error of the standardized mean difference (SMD) vs the SMD of all the studies on oxidative DNA damage shown in Table 5-Supplemental Material (in a fixed effects model to get the pseudo CI lines).



In the papers without report of SD this was estimated from the data as explained in the review and meta-analysis paper of Møller and Loft P 2010 (70).

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