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Susceptibility and vulnerability to health effects of air pollution: The case of nitrogen dioxide

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Abstract

Epidemiological and toxicological studies have reported adverse health effects in response to exposure to air pollution including nitrogen dioxide (NO_2). Some of these studies have indicated that specific populations may be at different risk of NO_2 related health effects than others. Adverse health effects from air pollution are not equally distributed among populations and individuals. Differences in vulnerability and susceptibility may affect the risk of developing a health effect and its severity.

A description and characterization of factors associated with vulnerability and susceptibility to health effects of ambient air pollution with a focus on NO_2 exposure, a common air pollutant which has been associated with human morbidity and mortality, is presented based on a scoping review for the period 2011-2015.

We identified epidemiological studies of factors that may play the role of effect modifiers of the association between exposure to NO_2 and related health effects. Studies that may influence risk were critically reviewed. Population groups and characteristics were identified and health effects described and put into the context of risk assessment of air pollution.

Population characteristics that can modify the health effects related to NO_2 and confer susceptibility are predominantly age, underlying disease, and potentially genetics and gender. These population characteristics don't differ from those identified for other air pollutants. Understanding about genetics and gender has been limited also in association with other air pollutants. Differential vulnerability has been shown due to socioeconomic factors. Insufficient attention in terms of exploration has been paid to the effects of other vulnerability factors.

Understanding how NO_2 may differently affect individuals or population subgroups is of major relevance for evidence-based policy making in emission reduction strategies and in health protection of those populations most vulnerable and susceptible.

1. Introduction

Air pollution is a global environmental health threat resulting in estimated more than 3 million deaths per year worldwide (Anenberg et al. 2010; Lelieveld et al. 2015). The common approach to assess the health effects using epidemiological data has been to assume that all persons are equally vulnerable and susceptible to air pollution. This assumption, however, very likely masks differences in health risks across population groups. Although average changes in population risk associated with exposure to air pollution are rather small, some individuals or groups are more vulnerable and/or susceptible than others. Therefore, in addition to their number it is relevant to also consider their characteristics. Differential vulnerability and susceptibility are linked to population characteristics that lead to differential exposure and associated distributional effects and effect modification (Makri & Stilianakis, 2008).

In epidemiological studies evaluation of differential health effects is done by estimating impacts related to clearly defined health outcomes and population stratification. Exposure assessments investigate population differences in behaviour, activity, underlying disease and the environment. Toxicological studies provide supporting evidence with respect to potential biological mechanisms in action. These factors may influence vulnerability and susceptibility and little has been done in their exploration as inter-related population factors.

2. Objective

This report aim at describing and characterising factors associated with vulnerability and susceptibility to health effects of ambient NO_2 exposure as a representative for urban air pollution. Nitrogen dioxide (NO_2) is a common air pollutant which has been associated with human morbidity and mortality (World Health Organization (WHO),

2013). Understanding how NO_2 may differentially affect individuals or population subgroups is of major relevance for evidence-based policy making in emission reduction strategies and protection of those most vulnerable and susceptible. Recommendations are noted in conclusion.

3. Background

Epidemiological studies have found associations between short-term exposure to concentrations of ambient NO_2 and short-term mortality and morbidity outcomes (WHO, 2013). Recent assessments of epidemiological studies related to health effects of long-term exposure to NO_2 also suggest an association between long-term exposure and respiratory and cardiovascular mortality (WHO, 2013; Faustini et al. 2014). To what extent the observed associations reflect adverse health effects that can be causally attributed to NO_2 has been heavily debated (WHO, 2013). The reason for that dispute is that NO_2 is correlated with other air pollutants, especially traffic-related pollutants, such as particulate matter (PM) of which the toxic effects are probably more pronounced. Therefore, there has been the notion that NO_2 may be a surrogate for PM produced by combustion. Cumulative epidemiological and toxicological evidence have amplified the association between exposure to NO_2 and adverse health effects (WHO, 2013).

3.1 Short-term health effects

Results from time-series epidemiological studies investigating the short-term health effects of NO_2 in recent years in Asia, Europe, and Canada have been added to the burden of evidence (Wong et al. 2006; Samoli et al. 2006; Brook et al. 2007; Chiusolo et al. 2011; Chen et al. 2012). In a quantitative systematic review of the evidence provided by time-series analysis focussed on the associations between short-term exposure to NO_2 and mortality and hospital admissions of respiratory and

cardiovascular diseases Mills et al. (2015) concluded that there is substantial evidence of the above association. A 10 μg/m^3 increase in 24h NO_2 was associated with increases in all-cause, 0.71%, (95% CI 0.43%-1.00%) cardiovascular mortality, 0.88% (95% CI 0.63%-1.13%) and respiratory mortality 1.09% (95% CI 0.75%-1.42%). With respect to hospital admissions the corresponding increases were 0.57%, (95% CI 0.33%-0.82%) for respiratory and 0.66%, (95% CI 0.32%-1.01%) for cardiovascular diseases. Their analysis of 204 studies provides estimates at the regional and global level observing regional heterogeneities needing further investigation. The meta-analysis results support previous findings on the independence of NO_2 health effects from other health pollutants, and provide estimates for further exploration and strengthening of that conclusion.

3.2 Long-term health effects

Previous assessments of the long-term health effects of exposure to NO_2 concluded limited evidence predominantly due to the availability of small number of studies (WHO, 2005). The WHO review of evidence on health aspect of air pollution (REVIHAAP) (WHO, 2013) addressed this issue again and evaluated recent studies on long-term exposure to NO_2. In addition, the question whether NO_2 may be a surrogate for other air pollutants was also taken into consideration. The WHO review concluded that it is still difficult to judge the independence of the NO_2 health effects in the long-term epidemiological studies given the strong correlation between concentrations of NO_2 and other traffic-related pollutants and supported by limited toxicological studies. However, the WHO report also points to epidemiological studies, which suggest associations of long-term NO_2 exposures with respiratory and cardiovascular mortality as well as with respiratory symptoms and lung function of children that were independent of other air pollutants, mainly, particulate matter mass metrics. The report clearly indicates that given the rather clear mechanistic evidence regarding the respiratory effects and the cumulative evidence from the short-term health effects studies a causal relationship is at least suggestive. The

review finally concludes that epidemiological studies are only one component in this assessment and stronger evidence should emerge from exposure and toxicological studies.

Recent epidemiological studies have shown associations of NO_2 concentrations and health outcomes. For instance, in a large cohort study Andersen et al. (2012) detected an association between long-term mean NO_2 levels at residence and non-specified and ischemic strokes. For incidence stroke and stroke hospitalisations followed by death within 30 days the hazard ratios (HR) were increased but not statistically significant 1.05 (95% CI 0.99-1.11), and 1.22, (95% CI 1.00 – 1.50) respectively. A case-control study focussing on the same association could confirm the association for short-term exposures but it could not identify any relation to stroke risk of medium term exposures (Johnson et al., 2013). Rivera et al. (2013) found that long-term traffic related exposures expressed in NO_2 concentrations were associated with subclinical markers of atherosclerosis. In the same cohort study a positive association between long-term exposure to NO_2 and systolic blood pressure were shown. A 10 $\mu g/m^3$ increase in NO_2 levels was associated with an increase of 1.34 mmHg of systolic blood pressure (95% CI 0.14-2.55) (Foraster et al. 2014).

Approaches looking at the combined exposure to PM and NO_2 have been more on the focus when adverse health effects of NO_2 were investigated (Mölter et al. 2013; Mölter et al. 2014; Chan et al. 2015). The strong correlations observed between these pollutants make the assessment of the independent contribution of NO_2 difficult, although NO_2 seems to be a good indicator of spatial variation in exposure to outdoor urban air pollutant mixture (Levy et al. 2014). The Dutch environmental longitudinal study showed that after adjustment for individual and area-specific confounders, for each 10 $\mu g/m^3$ increase, PM_{10} and NO_2 were associated with non-accidental mortality, (HR = 1.08, 95% CI 1.07-1.09 and HR = 1.03, 95% CI: 1.02-1.03, respectively), respiratory mortality (HR = 1.13, 95% CI 1.10-1.17 and HR = 1.02, 95% CI: 1.01-1.03, respectively), and lung cancer mortality (HR = 1.26, 95% CI 1.21-1.30 and HR = 1.10, 95% CI 1.09-1.11, respectively) (Fischer et al. 2015). In the context of

combined exposure to NO_2 and PM long-term improvement of air quality was associated with positive effects on lung function growth of children and adult lung function (Gauderman et al. 2015; Adam et al. 2015). Similar results for lung cancer were observed when, besides PM and NO_2, black smoke was added to the traffic-related exposures (Hart et al. 2015).

In a systematic review approach Faustini & Forastiere (2014) investigated the long-term effects on mortality of outdoor NO_2 and PM and carried out a meta-analysis of both NO_2 and PM health effects providing pooled estimates on mortality. Their results show that there is an effect of NO_2 on mortality and it seems to be as strong as that of PM with a diameter <2.5 μm ($PM_{2.5}$). For an increase of 10 $\mu g/m^3$ in the annual NO_2 concentration the pooled effect on mortality was 1.04 (95% CI 1.02-1.06) and 1.05 (95% CI 1.01.-1.09) for $PM_{2.5}$. The effect of NO_2 on respiratory mortality was 1.03 (95% CI 1.0 -1.03) and 1.05 (95% CI 1.01-1.09) for $PM_{2.5}$.

The quantitative assessment of the association between exposure to NO_2 and adverse health effects should stronger include vulnerable and susceptible populations since they are at increased risk of morbidity and mortality associated with increased exposures to air pollution. Thus, in addition to the number of people affected we should also consider their characteristics. Air pollution impacts are greater for people that are more susceptible, more exposed or otherwise more vulnerable. In what follows we explore the scientific output on this question focussing on how our knowledge has improved with respect to the adverse health effects of exposure to NO_2 of vulnerable and susceptible populations.

4. Rationale

Within populations the risk and the severity of adverse health effects associated with exposure to air pollution isn't uniform distributed. Some population groups and

individuals are more vulnerable and susceptible that others. Exposure changes may impact several groups differently. Even small changes in overall risk may have a disproportionate large impact on the health of certain populations. This implies that reduction of air pollution levels will result in unevenly distributed benefits. Risk assessment to better include differential vulnerability and susceptibility can lead to better understanding of the adverse health effects and to improved environmental justice. We focus on vulnerability and susceptibility to NO_2 health effects due to its important role in traffic-related air pollution especially in urban environments.

5. Policy relevance

Although ambient concentrations of air pollution have been reduced in Europe due to emission control and abatement current concentration of several air pollutants such as PM, Ozone and NO_2 remain still at levels that cause adverse health effects (WHO, 2013). Vulnerable and susceptible populations are at increased risk of morbidity and mortality associated with increased exposures to air pollution. This accounts in particular for urban settings and communities affected by traffic-related air pollution. Nitrogen dioxide (NO_2) is a typical pollutant of outdoor urban air pollution. Assessment of differential vulnerability and susceptibility to NO_2 can be of major help in understanding the impact of different exposures on health. Population vulnerability and susceptibility may provide useful insights into factors contributing to the heterogeneity of NO_2 health effects be short- or long-term. The assumption that all persons have identical sensitivity to air pollutants including NO_2 is profoundly a mean of simplification and it may not reflect the differences in health risks across populations. Evidence regarding which population groups are most vulnerable and susceptible will allow a better estimate of the health risks these groups are exposed. Moreover, capturing the particularities of vulnerability of specific populations may lead to health protection measures tailored to those populations. Differential

vulnerability may also apply to geographic regions. In this report we frame the issue specifically for NO_2 considering it as a major indicator for urban air pollution.

6. Susceptibility and vulnerability to air pollution health effects

Within the context of health, vulnerability is a term commonly used to describe the degree to which a population or an individual is unable to cope with the impacts of a health threat. With respect to air pollution associated adverse health effects, WHO specifies vulnerable population groups according to innate factors, acquired environmental, social or behavioural factors and unusually high exposures (WHO, 2004). This definition distinguishes between innate and acquired and represents a rather broad definition of vulnerability. However, acquired factors may be biological in nature, as is the case of underlying diseases. Both age and underlying disease are associated with physiological capacity to cope with air pollution but age is an innate factor while underlying disease is an acquired. Moreover, the level of exposure could also be influenced by behaviour associated with age (innate factor) and occupation or housing characteristics both (acquired factors) (Marki & Stilianakis, 2008). WHO considers as vulnerable groups young children, elderly, person with certain underlying diseases, foetuses, groups exposed to other toxicants and interact with air pollutants and those with low socioeconomic status (WHO, 2004).

In general, and in the context of air pollution health effects vulnerability has been used to define acquired factors such as socioeconomic status, access to health care and differential exposure. Differential exposure can be the result of occupational exposure (e.g. outdoor work) or residential location (e.g. proximity to high traffic) and therefore exposure to high concentration of certain air pollutants.

The other term commonly used in this context is susceptibility. It refers to factors such as age, gender, genetic profile, pre-existing diseases and thus to individual characteristics that may increase risk through a biological mechanism in action.

Susceptible populations are often determined by the characteristics of the exposure (type, timing) and the associated health effects (type, long-term, short-term) (Künzli 2005; Pope 2000). Very often populations are affected by air pollution in ways that are not life-threatening in short term, and therefore effects cannot be observed and reported immediately. Clinical symptoms may be short-term, almost unnoticed, but they may also be transient and/or reversible (e.g. decreased lung function). However, they can have long-term implications if exposures are continuous. Short-term exposure to high concentration of air pollutants may advance death by days or weeks. Long-term exposure may lead to conditions that reduce life expectancy. Moreover, the interaction of short and long-term exposures can lead to a situation where exposures to high concentration for a short period may lead to advance mortality in persons with underlying diseases related to long-term exposure (Künzli, 2005).

Very often and unfortunately the two terms vulnerability and susceptibility have been used interchangeably causing confusion. To avoid misunderstandings new terminology has been coined using terms such as effect modifiers, or response-modifying factors (Vinikoor-Imler, 2014). Nevertheless, the two terms should be kept apart. Susceptibility implies a greater risk of a health outcome at any specific level of exposure while vulnerability refers to a greater likelihood of being exposure including being exposed to higher concentrations of air pollutants (Samet 2014).

7. Susceptibility and vulnerability to NO_2 health effects

7.1. Methodology

A scoping review of the scientific evidence was conducted to provide an overview of the progress made in recent years with respect to the characterisation of the vulnerability and susceptibility to health effects associated with short or long-term

exposure to NO_2. We focussed on the review of epidemiological studies. We adapted the scoping review process (Arksey & O'Malley, 2005) since our question is rather broadly defined and allows us to consider various study designs. To minimise the risk of bias for individual studies we used elements of the PRISMA methodology for the implementation (Moher et al. 2009).

We searched the National Library of Medicine's MEDLINE database through PubMed (NIH PubMed, 2015) for epidemiological studies of exposure to NO_2 and associated health effects that explicitly looked at vulnerability and susceptibility of population groups. Our search covered the period 2011-2015 and the articles had to be written in English, be peer-reviewed and be indexed by Nov, 19, 2015. The search included the terms nitrogen dioxide, air pollution, susceptibility, vulnerability, susceptible, vulnerable, effect modifier(s), effect modification, effect modifying. Our PubMed search identified 103 publications. After a first screening of title and abstract 31 publications were retained for further review. The rest was removed since they didn't fulfil all criteria.

We could identify very few studies that could show some evidence for the adverse health effects of NO_2 with respect to vulnerability and susceptibility independent from other highly correlated air pollutants. Therefore, we assessed the results that explored an independent effect from NO_2 together with the results that investigated effects that could partially be attributed not only to NO_2 but also to other air pollutants such as to PM or O_3. However, particular emphasis was given when the specific independent effect of NO_2 could be detected.

7.2 Age

Elderly, children and foetuses as well as pregnant women have been shown to be more susceptible to adverse health effects of air pollution.

Foetuses - Pregnant women

Epidemiological studies looked at the association between preterm birth (< 37 weeks of gestation) and ambient air pollution. A study in the U.S. State of Georgia was conducted over the period 2002-2006 to assess the risk of 11 air pollutants, among them NO_2 (Hao et al. 2015). All traffic related pollutants including NO_2 were associated with preterm birth. For NO_2 the odds ratio (OR) for interquartile range increase in first trimester was 1.009, (95% CI 1.005-1.013) but also for the second and third trimester a relationship could be shown. Associations were higher for pregnant women with low education status. For the same health outcome a study in California showed very similar results with increased OR for early preterm birth for those exposed to the highest quartile of each traffic-related pollutant including NO_2 during the second trimester and the end of pregnancy (Padula et al. 2014). Also associations were stronger among pregnant women living in low socioeconomic status neighbourhoods. In an assessment of the association between foetal growth and NO_2 concentrations at mother's home showed that the risk of small weight and small head circumference for gestational age were reduced (OR 0.70, 95% CI 0.53-0.92; OR 0.76, 95% CI 0.56-1.03 respectively) for an increase of 8.8. $\mu g/m^3$ of NO_2 (Bertin et al., 2015). Residence-based factors (urban-rural) modified the effect of air pollution for small head circumference for newborn boys. These studies show the inter-relationship between susceptibility and vulnerability factors as effect modifiers.

Short-term effects on blood pressure of pregnant women were attributed to air pollution, including NO_2, in combination with ambient temperature. Elevated NO_2 levels before the blood pressure measurement were associated with reduced systolic blood pressure (Hampel et al. 2011). Decreased temperature led to an increase in systolic blood pressure whereas elevated NO_2 levels before the blood pressure measurements were associated with reduced blood pressure. On the other side and in the same study, PM was associated with increased systolic blood pressure. Vulnerability captured through the social, demographic and life-style factors may

affect the health of pregnant women. In particular younger women with low social status are exposed to higher NO_2 levels (very often above the European reference limit of 40 µg/m^3) whether they are measured outside their homes or when time-activity patterns are taken into account. (Llop et al. 2011).

Children

Numerous studies of different air pollutants, including NO_2, suggest different health impacts for children at all ages (e.g. early childhood, adolescents) at different exposure levels and locations. Recent studies, some of them specifically looking at the independent impact of NO_2, confirm these effects which are predominantly of respiratory nature such as persistent cough, wheezing and asthma. Air pollutants concentrations have been associated with asthma exacerbations in children with larger effects among preterm born children indicating variation in their susceptibility very early on (Strickland et al. 2014). Susceptibility to respiratory disease is particularly critical during the first year of life. Assessment of the relation between prenatal and postnatal NO_2 levels and the development of lower respiratory tract infections, wheezing and persistent cough during first year of life showed high levels of the cumulative incidence of the above clinical diagnoses. Moreover, for an increment of 10 mg/m^3 in postnatal outdoor NO_2 concentration the OR was 1.40 (95% CI 1.02-1.92) for persistent cough (Esplugues et al. 2011). Similar effects of PM and NO_2 were observed in kindergarten children with increased levels of NO_2 concentration be associated with increased prevalence of allergic rhinitis (OR 1.96 95% CI 1.27-3.02) among girls in kindergarten. Prevalence of respiratory symptoms was higher among children living near busy roads, and factories with a particularly strong effect among girls (Liu et al. 2013).

Effect modification of the respiratory effects of air pollution in children could be attributed to breastfeeding. Non-breastfed children for a 10 µg/m^3 increase of NO_2 had an OR of 1.40 (95% CI 1.19-1.64) for cough 1.41 (95% 1.16-1.71) for phlegm, 1.17 (95% CI 1.00-1.36) for current wheeze, and 1.25 (95% CI 1.07-1.46) for doctor-

diagnosed asthma. For breastfed children the corresponding OR's were 1.25 (95% CI 1.09-1.43) for cough, 1.15 (95%CI 0.99-1.34) for phlegm, 0.97 (95% CI 0.87-1.08) for current wheeze and 1.17 (95% CI 1.05-1.32) for doctor-diagnosed asthma. These results indicate that breastfeeding may reduce the susceptibility to certain respiratory diseases (Dong et al. 2013).

Traffic-related air pollution and specifically NO_2, used as a surrogate, have been linked to childhood asthma. Allergic diseases have been identified as potential effect modifiers. Presence of other allergic disease in children and birth and cumulative NO_2 were associated with lifetime asthma and wheeze. The effects in children without allergic disease were weaker or non-existent. This association suggests that allergic sensitization may be part of the biological mechanisms in action of traffic-related air pollution initiated asthma (Dell et al. 2014). A susceptibility factor may also be local or systemic inflammation in combination with oxidative stress. Inflammatory markers such as whole blood cytokine responsiveness have been used to show the modifying effects of systemic inflammation. It could be shown that exposure of asthmatics to NO_2 was associated with higher production of pro-inflammatory cytokines. No association could be found in non-asthmatic children. Similar results could be shown for NOx, PM indicating an association between cytokine responsiveness and traffic related air pollution in asthmatic children (Klümper et al. 2015). Asthma morbidity related to air-pollution seems to be affected by age as a susceptibility factor with school children to be at the highest morbidity risk (Alhanti et al. 2015).

Long-term exposure to air pollution may affect lung function of children. Long-term improvements in air-quality were associated with positive effects on lung function growth in children. Declining levels of NO_2 were associated with improvement of lung function variables in children also in those with asthma (Gauderman et al. 2015). Concentrations of NO_2 assessed to early and grown-up life (birth, 5 and 15 year) home addresses were not associated with lung function variables. However, among

asthmatics several lung function variables were negatively associated with long-term NO_2 concentrations pointing to the susceptibility of asthmatics (Fuertes et al. 2015).
A major European multicenter study of five birth cohorts of air pollution exposure and childhood asthma prevalence could not identify a significant association between air pollution exposure and childhood asthma prevalence. For NO_2 the adjusted OR was 0.88 (95% CI 0.63-1.24). An independent effect of NO_2 was not investigated (Mölter et al. 2015).

Elderly

Exposure to air pollution of elderly populations may lead to higher morbidity and mortality predominantly due to cardiovascular and respiratory disease (Hoek et al. 2013). Compromised physiological capacity due to age associated factors of older people doesn't allow them to cope with air pollution as other age groups. Thus, elderly show a differential susceptibility to air pollution due to effects of prior high exposures, weakened immune responses and higher prevalence to underlying disease (Sandström et al., 2003).
Risk assessment of hospitalization and mortality from cardiovascular disease due to exposure to ambient air pollution showed that short-term exposure to air pollution was associated with acute myocardial infarction. These associations were also attributed to increased levels of NO_2 concentrations. For an increase of 10 µg/m^3 of NO_2 concentration the OR was 1.022 (95% CI 1.004-1.041) for acute myocardial infarction hospitalizations. A clear susceptibility effect for elderly persons (>75 years) and older patients with hypertension and chronic obstructive pulmonary disease among others could be detected (Nuvolone et al. 2011). The association of NO_2 concentrations and mortality in particular of elderly people could also be confirmed in other geographical regions such as China (Chen et al. 2012). The association with mortality accounts in particular for older people with chronic obstructive pulmonary disease making them more susceptible (Faustini et al. 2012).

The long-term effects of exposure to traffic related air pollution with respect to asthma onset is less investigated. Using exposure to annual NO_2 levels as proxy for traffic related air pollution over a period of 35 years NO_2 levels were associated with the risk of asthma hospitalizations in older people for first-ever admissions and for the full cohort (first-ever admission and readmissions). Moreover, those with underlying disease and previous asthma or chronic obstructive pulmonary disease hospitalizations were more susceptible (Andersen et al. 2012).

Exposure to air pollution of elderly is associated with reduced lung function. Subchronic exposure to NO_2 has been associated to decreases in certain variables of lung function such as forced vital capacity and forced expiratory volume in 1s. Epigenetic mechanisms may influence this association indicating their potential for effect modification (Lepeule et al. 2014).

7.3 Underlying disease

Cardiovascular disease, chronic lung disease, ischemic heart disease, heart rhythm disorders, heart failure, asthma, diabetes, they all have been associated with a strong susceptibility to air pollution. They compromise organ function and overall ability of the human body to respond to exposure. These diseases are usually linked to advanced age. However, pre-existing disease in children and adults can also enhance susceptibility to air pollution. Asthma in children, as discussed above, is of particular concern since exposure to air pollutants and particularly NO_2 may exacerbate respiratory symptoms (Künzli 2005). Underlying diseases could be identified as potential effect modifiers of air pollution health effects by investigating individual socio-demographic characteristics and chronic or acute medical condition in the association between NO_2 concentrations and cause-specific mortality. With a 10 $\mu g/m^3$ increase of NO_2 there was an increase of 2.09% (95% CI 0.96%-3.24%) for natural mortality and higher mortalities for cardiac or respiratory disease 2.63%, (95%

CI 1.53%-3.75%) and 3.48%, (95% CI 0.75%-6.29%) respectively (Chiusolo et al. 2011). Moreover, these associations were independent from those of PM10 and Ozone. The more the specific chronic condition the stronger were the associations. Ischemic heart disease, pulmonary circulation impairment, heart conduction disorders, heart failure and diabetes seemed to confer a strong susceptibility to air pollution. Long-term exposure to traffic-related air pollution using NO_2 concentrations could contribute to the development of chronic obstructive pulmonary disease (hazard ratio 1.08, (95% CI 1.02-1.14) where people with diabetes and asthma may show enhanced susceptibility (hazard ratio 1.29, 95% CI 1.05-1.50 and 1.19, 95% CI 1.03-1.38 respectively) (Andersen et al. 2011).

Effect modification by cardiac diseases could be shown in stroke mortality due to air pollution. The association between NO_2 levels and ischaemic stroke mortality among people with cardiac diseases was stronger that those without underlying cardiac diseases. An increase of 10 $\mu g/cm^3$ of NO_2 was associated with an increase of 7.05% (95% CI 1.92-12.17) in ischeamic stroke mortality for people with underlying cardiac condition and 0.60% (95% CI 0.49-1.68) for those without (Qian et al. 2013). Effect modification by other pre-existing diseases such as hypertension or diabetes could not be identified in this study.

The association between cardiac mortality and air pollution has been established in many studies. However, interestingly they couldn't be shown in some studies in particular when cardiac susceptibility to acute exposure of NO_2 was investigated. Patients with coronary heart disease and impaired left ventricular systolic function didn't show changes in heart rate, blood pressure or heart rate variability measured after exposure to NO_2 compared to several other air pollutants (Scaife et al. 2012). These and similar findings led to the hypothesis that the associations found by other studies may be due to other strongly correlated air pollutants such as PM.

7.4 Genetics

The variability of human responses to air pollutant exposure within and across populations has been attributed to individual genetic background (Kleeberger 2005). The links between environmental exposure and genetic factors are highly complex, variable and not sufficiently understood. Genes associated with immune dysfunction and lung inflammatory response may be associated with effects from gaseous pollutants (Kleeberg 2005). Exposure to air pollution including NO_2 has been associated with insulin resistance an underlying mechanism and a marker for diabetes mellitus. The association was stronger among those with certain genotypes potentially increasing susceptibility (Kim & Hong 2012). Gene variants related to oxidative stress and inflammation may impact association between air pollution and childhood asthma. Children with a certain genetic profile were at increased risk of current asthma OR 2.59 (95% CI 1.43-4.68) for 10 µg/m^3 of NO_2 and ever asthma (OR 1.64, (95% CI 1.06 - 2.53) compared with carriers of a different genetic profile (OR 0.95 (95% CI 0.68-1.32) for current asthma and 1.20, (95% CI 0.98-1.48) for ever asthma respectively (MacIntyre et al. 2014). The results were partially not statistically significant though and therefore should be seen as an indication that children carrying certain alleles may be a potential susceptible population but this has to be confirmed by further research.

7.5 Gender

Whether men and women differ in their responses to air pollution exposure is an open question. Findings are very limited and inconclusive. We couldn't identify any recent specific study on that issue. Previous work has shown that women may be at higher risk for respiratory symptoms, and diminished lung function with asthmatic women being more susceptible (Annesi-Maesano et al. 2003). Most studies are

conducted in the context of reproductive outcomes and are related to health effects of pregnant-women with an emphasis rather on the effects on children with the effects on women to be a secondary result as addressed above. It may be useful to specifically address this issue for young women looking at this issue from the prevention perspective.

Recent studies looking at susceptibility factors in a broader context could identify some associations between gender and air pollution with males to be more susceptible (Son et al. 2012). Effects were attributed to several air pollutants including NO_2 but not specifically to NO_2.

7.6 Social coping

Extrinsic factors such as socioeconomic status are part of the vulnerability burden of subpopulations exposed to air pollution. Epidemiological studies often treat socioeconomic status as a confounder since it correlates with other variables that modify risk. However, in studies where socioeconomic factors where included as effect modifiers a relationship between income or education and in general socially disadvantaged people could be shown (Ponce et al. 2005; WHO 2003).

Also in recent studies could be shown that, for instance, for socially disadvantaged elderly the risk of dying on days of higher air pollution increases. An association between education status of elderly and exposure to increased air pollution was detected indicating that concentrations deemed acceptable for the general population may not protect susceptible groups (Cakmak et al. 2011). Similar results related to the modifying effect of education were obtained in another recent study in Brasil where for all-cause mortality effects estimates for those with higher education were lower than for those with no education for exposure to NO_2 1.66% (95% CI 0.23%-3.08%), among other pollutants (Bravo et al. 2015). In the context of the effects of short-term NO_2 variations on all-cause mortality the effect modification by

neighbourhood characteristics was explored. People living in the most deprived neighbourhood were more vulnerable to air pollution episodes compared with residential areas with higher socioeconomic status (excess risk 3.14%, 95% CI 1.41%-4.90%) (Deguen et al. 2015). These results imply that people living in deprived areas are likely to be even more vulnerable to chronic exposure to air pollution, including higher NO_2 concentrations.

8. Discussion

Aim of this scoping review was to describe the role of differential vulnerability and susceptibility for health risk assessment due to air pollution. We focussed our review on recent evidence from epidemiological studies on the health effect of NO_2 since it is considered a major representative of urban and traffic-related air pollution. Although short-term health effects of exposure to NO_2 have been demonstrated adverse health effects related to long-term exposure are still debated. The reason for this inconclusiveness may be the fact that NO_2 concentrations are highly correlated with those of other air pollutants such as PM and Ozone and its independent effects are difficult to be demonstrated. Evidence coming from short term epidemiological studies has been convincing. For long-term effects evidence still needs to accumulate.

Exposures to air pollution may have different effects on individuals and population groups due to differences in innate and acquired characteristics such as age, genetics, underlying disease, socioeconomic status. Innate characteristics are mainly biological and physiological and reflect the capacity of the human body to respond to exposure and confer susceptibility. Acquired factors such as socioeconomic status are those who affect social coping capacity and do not allow the individual or the population group to minimize exposure and confer vulnerability.

Populations associated with differential susceptibility to air pollution are foetuses, pregnant women, children, elderly and persons with underlying diseases. Differences between man and women as well as genetic profile may also be part of differential susceptibility with currently limited evidence supporting this notion. Socioeconomic factors such as income, education, residential area, may also affect health risk to air pollution.

Individual population characteristics encompass several factors that relate to more than one feature of vulnerability. For instance, an elderly can be more susceptible due to his medical condition compared with another elderly and due to differences in socioeconomic status. For instance, elderly with underlying disease living in a less polluted residential area, and/or having a higher educational, or income level may have better access to health care, public health information, and social infrastructure making them less vulnerable to air pollution. Thus, inter-relationships should be taken into account so that the relative influence of vulnerability and susceptibility on populations groups can be better evaluated (Makri & Stilianakis, 2008).

Vulnerability and susceptibility of certain populations to air pollution health effects is expected with respect to all air pollutants although their relative importance in the health effects may differ depending on the differential profile of the population group or the individual.

The majority of the studies to date have focussed more on susceptibility factors and less on socioeconomic and other vulnerability factors. This review indicates that the relationship between certain susceptibility factors and differential risk encompasses other pathways of vulnerability too. Identification of these factors may lead to more targeted interventions, such as, improving management of chronic diseases, minimising pollution levels and exposure at specific places, e.g., nursing homes, or at the local level. For example, risk differences are often identified for children but the influence of activities and behaviour at different developmental stages, quality of school and home environments, or commuting to and from school could also point to differential risks where specifics interventions may be considered. These

interventions could be improvement of air quality in school environments better information, behavioural changes.

Thus, characteristics of certain populations may inform risk management and support the development of policy and health protection strategies tailored to the needs of those populations. Consideration of vulnerable and susceptible groups in risk assessments or air pollution can contribute to the understanding of how the benefits of air pollution reduction are distributed within a population.

9. Conclusions

Health effects such as all-cause, cardiac, and respiratory mortality, due to exposure to NO_2 in ambient air have been confirmed in recent epidemiological studies that investigated the short-term health effects of NO_2. Moreover, these studies also suggest an independent effect of NO_2. Although long term studies indicate similar effects of NO_2 on health the independence of those effects from other pollutants is difficult to be shown because of the strong correlations between NO_2 and other pollutants.

Air pollution health risk assessment, including that of NO_2, usually assumes that all individuals and populations groups are equally susceptible and vulnerable. Recent research shows that there are population characteristics that interact and confer differential susceptibility and vulnerability. Understanding susceptibility and vulnerability factors would allow the prioritisation of further research and action plans.

Given that factors affecting susceptibility and vulnerability lie in different scientific fields such as epidemiology, exposure science, social science an integrated approach should be followed.

Some population groups haven't been investigated sufficiently, e.g. pregnant women, differential susceptibility of men and women. Vulnerability factors such as socioeconomic factors have received limited attention.

Effect modification due to differential susceptibility and vulnerability may lead to better public health interventions to protect population groups from disproportionate exposures and health effects leading to better environmental justice.-

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