Mortality endpoints

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Tentative title: Effects of long-term exposure to air pollution on natural cause and cardiovascular mortality

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If you have any questions about the protocol, please contact the aim leader (Gerard Hoek: g.hoek@uu.nl; telephone +31 30 2539498)

Background

In the cohort studies assessing effects of long-term exposure to air pollution on mortality, it has generally been found that effects were stronger for cardiovascular causes of death than for other causes of death (excluding respiratory disease and lung cancer) (Beelen et al, 2009; Beelen et al. 2008; Nafstad et al. 2004; Pope et al. 2002; Laden et al. 2006; Ostro et al. 2011). A recent study from the US in higher educated men did not find any association between PM2.5 and cardiovascular disease mortality (Puett et al. 2011). Studies have evaluated the broad category of all cardiovascular diseases combined, for reasons of cohort size or the limitations of death certificates to define causes of death more specifically. In some of the US studies, cardio-pulmonary mortality was analysed – combining cardiovascular and respiratory disease (Pope et al. 2002). In ESCAPE we will analyse natural cause, cardiovascular and respiratory mortality separately. Studies in the US have mostly reported associations with PM2.5 (Brook et al. 2010). Studies in Europe have also reported associations between long-term exposure to NO_2 or NOx and cardiovascular mortality, including studies in the Netherlands (Beelen et al. 2008), France (Filleul et al. 2005) and Norway (Nafstad et al. 2004).

The findings of the cohort studies are consistent with time series studies documenting short-term associations between air pollution and cardiovascular mortality and hospital admissions (Brook et al. 2010). Several plausible mechanisms

have been proposed to explain the mortality effects of ambient air pollution (Brook et al. 2010). The diversity of diseases included in the broad category cardiovascular disease, makes it unlikely that the air pollution risk is the same for all diseases. Studies have therefore evaluated more specific cardiovascular causes.

Several studies have assessed ischemic heart disease (IHD), including myocardial infarction (Pope et al. 2004; Nafstad et al. 2004; Beelen et al. 2008). IHD is one of the most prevalent causes of death worldwide. In the Women's Health Initiative Observational Study, an increase of 10 $\mu g/m^3$ was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). CVD events were defined as deaths from MI, CAD, and coronary revascularization (Miller et al., 2007). Data from the Nurses' Health Study obtained from 66,250 women showed that a 10 $\mu g/m^3$ increases in 12 month average exposure to PM_{10} were associated with increased all cause mortality (16%; 95% CI: 5 to 28) and fatal Coronary Heart Disease (43%; 95% CI: 10, 86). Three studies in Sweden and Italy reported an association between long-term exposure to NO_2 and myocardial infarction, with most of the effect limited to fatal MIs (Rosenlund et al. 2006; Rosenlund et al. 2008; Rosenlund et al 2009).

There is also evidence from ecological studies that stroke (cerebrovascular) mortality is associated with ambient air pollution and traffic exposures (Maheswaran and Elliott 2003; Maheswaran et al. 2006). Cohort studies have not found consistent associations with stroke (Beelen et al 2009; Brook et al. 2010). Time series studies have reported somewhat inconsistent associations between daily variation of air pollution and stroke mortality and hospital admissions. In these studies, no difference was made between hemorraghic and ischemic stroke, diseases which likely will have different associations with air pollution. However, death certificate information on type of stroke is not complete and reliable.

Few studies have also found associations with less prevalent causes of death, including, dysrhythmia and heart failure (Beelen et al. 2009). A subsequent analysis of the ACS cohort study found that long term exposure was most strongly associated with mortality attributable to ischemic heart disease, dysrhythmia, heart failure, and cardiac arrest (Pope, Burnett et al. 2004). Plausibility of arrhythmia associations is supported by associations reported between defibrillator discharges and air pollution (Peters, 2001; Dockery, 2006).

For cardiovascular mortality, the issue of disentangling effects of air pollution and traffic noise is important. The large ESCAPE dataset will allow us to do this with more power than the single studies looking at joint exposures so far (Beelen et al. 2009; Selander et al. 2009). For the cohorts which are also included in WP5 we will have noise exposure assessment which allows us to assess independent effects of air pollution and noise.

Studies have provided some clues for effect modification. At least three studies have shown air pollution effects to be larger in subjects with lower education (Pope et al. 2002; Beelen et al. 2008; Krewski et al. 2009). This effect is not well-understood and also not very consistent as evidenced by the much smaller difference in PM2.5 relative risk across educational groups in the recent analysis of the ACS study (Krewski, 2009) compared to the original paper (Pope, 2002). In a Swedish study there was a tendency towards higher effect estimates on IHD for the more affluent population (Rosenlund et al. 2009). In the Dutch cohort, there were also suggestions that air pollution risks were larger in never-smokers and subjects with low fruit consumption (Beelen et al. 2008). Never smokers with higher body mass index were at greatest risk of fatal CHD in the Nurses Health study (Puett et al., 2008).

Hypotheses

1. Air pollution at the residence is associated with risk for development of mortality
2. The association between air pollution and mortality is stronger among non-smokers, subjects with a low fruit intake, subjects with low education and subjects with high body mass index.
3. An association between air pollution and mortality is stronger for ischemic heart disease, stroke and arrhythmia than for all cardiovascular disease combined.

Contributing cohorts

Contributing cohorts will be HUBRO, E3N, SIDRIA, DCH, VHM&PP, SNAC-K, SALT/Twin gene, 60-y/Improve, SDPP, SAPALDIA, KORA, FINRISK, SALIA EPIC-Italy cohorts (three separate cohorts), EPIC-Netherlands (two separate cohorts), EPIC-Greece, EPIC-Oxford, EPIC-Umeå, EPIC-Heidelberg (possibly), EPIC-San Sebastian.

Outcome definition

Outcomes are defined on the basis of the underlying cause of death recorded on the death certificates. Cause of death will be coded on the ICD-9 or ICD-10 classification of diseases (Table).

Cause	Codebook name	ICD-9 codes	ICD-10 codes
Natural cause mortality	Natumort_w6a4	001 – 779	A00 – R99
All cardiovascular	cvdmort_w6a2	400 – 440	I10 – I70
Ischemic heart disease (IHD)	ihdmort_w6a2	410 – 414	I20 – I25
Myocardial infarction	mimort_w6a2	410	I21, I22
Cerebrovascular (stroke)	cbvmort_w6a2	430 – 438	I60 – I69
Cardiac dysrhythmia	cdmort_w6a2	427	I44 – I49

Check carefully the code of death information, e.g. missing values for subjects of whom we know they have died. A small percentage of missing codes will be treated by coding these cases to a non-event and censoring at date of death. Please document the number and percentage of cases with missing cause of death information.

Cohort members who die from non-natural causes should be censored at time of death.

Exposures

For all endpoints we will use the annual average concentration at the residential (baseline) address of the following components (between brackets the variable names as in codebook):

- $PM_{2.5}$ (pm25)
- PM_{10} (pm10)
- PM_{coarse} ($PM_{10} – PM_{2.5}$) (pmcoarse)
- Absorption coefficient $PM_{2.5}$ (pm25abs)
- NO_2 (no2)
- NO_X (noX)
- Traffic intensity of the nearest street (trafnear) combined with and without background NO2 (no2_bg)

- Total traffic on all major roads in a 100m buffer (trafmajorload_100) combined with and without background NO2 (no2_bg)
- Back-extrapolated concentrations will also be analysed in sensitivity analyses (for variable names see codebook)

Potential confounders (baseline data – unless otherwise specified)

We analyze data using 4 models with different sets of potential confounders adjusted for:

Model 1: gender, calendar time

Model 2: model 1 + smoking status, smoking intensity, smoking duration, environmental tobacco smoke (ETS), body mass index, occupation, intake of fruit, alcohol consumption, marital status, educational level, employment status, and intake of vegetables

Model 3: model 2 + socio-economic status (SES) at an area-level (e.g. of the municipality or neighborhood).

Model 4: model 3 + hypertension at baseline, physical activity, diabetes and cholesterol

Description of co-variates (between brackets the variable names as in codebook):

Note: _b means that these are baseline data, see codebook

Gender. Categorical variable. (sex_b) Female = 0; Male = 1

Calendar time. The year of enrolment. Analyzed as a linear variable for recruitment periods of approximately five years. In case of longer periods, separate linear terms will be used (calyear, not standard variable in dataset. Will be made in the statistical code)

Smoking status. Never (3), former (2), present (1). But reversed in code, so never is reference category Categorical variable. (smoking_b)

Smoking intensity. Continuous variable (g/day). Preferable, this variable is calculated as a life-time average tobacco smoking intensity with never smokers coded as zero (ncig_lif_w6). Preferable smoking intensity includes all types of tobacco smoking, summed up as cigarette equivalents where one cigarette equals 1 g of tobacco, 1 pipe equals 3 g, 1 cheroot equals 3 g and one cigar equals 4.5 g tobacco.

A good alternative is smoking intensity at enrolment (present smokers) and historically (former smokers).

Smoking duration. Continuous, linear variable (years). Ideally, smoking duration is the net number of smoking years, i.e. taking into account smoking breaks. Alternatively, simple calculations such as “age at stop minus age at start” for former smokers or “current age minus age at start” for present smokers will do. (smok_yrs_w6 or alternatively smok_dur_w6)

ETS. This variable is defined very different in the cohorts. Since ETS is a relatively weak risk factor for mortality, we will use a simple categorical indicator variable for exposure, such as yes/no to “room with ETS > 1 h/day”, “spouse smoking” or other cohort-specific definitions, which can divide the cohort participants properly. Another example is a dichotomous variable indicating no/low exposure: “no smoker in the home and ETS at work for less than 4 h/day” versus high (all others). (etsa_b and etsb_b)

Body mass index (BMI). Defined as weight/height^2 (kg/m^2). Non-linear associations have been reported with higher risks for low and high BMI. We will use therefore BMI and BMI^2 as two variables in the model. (bmi_b, bmi squared to be generated in script – bmi_b2).

Occupation. It differs between cohorts which (if) information is available. For cardiovascular disease which may be affected by a range of risk factors, we prefer a classification for being “blue collar” or “white collar” worker. The “occupation” variable must include information beyond “employment status” (see below for definition of “employment status”). If you have such information please contact the aim leader (Gerard Hoek). If available use as variable name “occupcollar”.

Intake of fruit. Ideally this variable is defined as “grams per day” (continuous, linear variable), which is possible in the DCH and the EPIC cohorts. However, other cohorts have information in a different format, such as categories, which is also acceptable. (fruit_b)

Alcohol consumption. Non-linear associations have been reported with higher risks for non-alcohol users and high amounts of alcohol. We will therefore use alcohol use (g/day) and alcohol use^2 as two variables in the model. (alc_current_b, alcohol use squared to be generated in script – alc_current_b2)

Marital status. The variable is preferably defined as: single (1), married/living with a partner (2), divorced/separated (3), widowed (4). (mar_stat_b)

Educational level. Categorical variable with categories such as: “primary school”, “secondary school and more” and “university degree”, or whatever is available and makes sense in each cohort. (edulev_b) Low = 1; medium = 2; high = 3, but reversed in code so high is reference

Employment status/affiliation with the labour marked. Categorical variable with categories such as employed, self-employed, unemployed, stay at home, and retired, or whatever is available and makes sense in each cohort. A dichotomous variable such as “unemployment during last year before enrolment (yes/no)” is also acceptable (occstatus_b).
Intake of vegetables. Ideally this variable is defined as “grams per day” (continuous, linear variable), which is possible in the DCH and the EPIC cohorts. However, other cohorts have information in a different format, such as categories, which is also acceptable (rawveg_b)

Area-level SES. This information exists as mean income, unemployment rate or other information. Further, data is available on neighborhood, municipality and/or regional scale. Data corresponding approximately to the enrolment period is preferred but data from a later period might be used as well. Definition of the variable as linear or categorical must be agreed upon with the specific aim leader on a case-to-case basis. Few cohorts have area-SES as part of their basic cohort data, but it is highly desirable that the local groups put effort into retrieving area-level SES data.

Hypertension at baseline. Categorical variable. Prevalent hypertension (systolic BP≥140 mmHg or diastolic BP ≥90 mmHg or antihypertensive medication) at baseline (hyper_p_b).
Physical activity. Continuous. Physical activity in metabolic equivalents (metcal_b). If not available, other physical activity variables are also acceptable.
Diabetes. Categorical. Defined as diabetes or impaired fasting glucose (blood glucose level >110 mg/dl or treatment with insulin or oral hypoglycaemic drugs (diab_b)
Cholesterol. Continuous. Preferably LDH and HDL separately (ldl_m and hdl_m).

A potential confounding issue might be differences between rural and urban areas in both air pollution and health outcomes. In the statistical protocol (page 11-12) text about this is provided. It should be evaluated locally whether this is an issue for the local cohort.

The included cohorts have different definitions of some co-variates, and not all cohorts have information about all co-variates. Each cohort must describe precisely their specific definition of each variable. Deviations from the models or the

specification of covariates (above) must be agreed upon with the specific aim leader (Gerard Hoek).

Analytic approach

Inclusions, exclusions and descriptive statistics

Each cohort sends descriptive statistics to the specific aim leader. In principle this is the information that will be documented in sheet 1 of the statistical script and Excel sheet.

Main analyses

Associations between air pollution and mortality will be analyzed in Cox models using age as the time scale to ensure that deaths are compared with cohort members of exactly the same age, providing perfect adjustment for age. Age is chosen as time scale (rather than calendar time) because age is a much stronger predictor for death than calendar time. Air pollution effects will be analyzed for all cardiovascular deaths combined and specific causes of death (see above for outcome definitions).

We will add to standard Cox models individual level confounders (model 2), and area-level potential confounders (model 3). An extended confounder model (model 4) will be used in sensitivity analyses. Based upon the results of the Torino workshop where it was shown that for the majority of cohorts, no random effect was found for the areas, we will ignore random effect in the main analysis. In a sensitivity analysis we will however check random effects again in all cohorts. Difficulty in fitting random effect Cox models in STATA and R contributed to this decision.

Censoring will occur at the time of a death (our endpoint), at the time of other deaths, emigration, disappearance, loss of follow-up for other reasons or at end of follow-up, whichever came first. See also above what to do if cases have missing cause of death information (section Outcome definition).

Only study participants without missing value in any confounder variable of model 3 will be included in any analysis.

“Unknown” counts as missing; we will not accept an “unknown” category to make the models run in spite of missing values.

We accept that up to 10% of the cohort members (after exclusions due to missing address/geocoding) are excluded due to a missing value in potential confounders; if more than 10% of the cohort members have missing value we will exclude variable(s) with many missing values from the models or, alternatively, establish evidence that selection bias is unlikely by comparing those (> 10%) with missing to those without missing in any variable. Please contact the aim leader if the percentage of missings is more than 10%.

Some covariates will be adjusted for in some but not other cohorts. In cohorts including these variables, we repeat the analyses (all cardiovascular deaths combined; each of the exposure variables) without adjustment for these variables to test the sensitivity to adjustment. These sensitivity analyses will be specified when we know exactly which cohorts will adjust for which covariates.

Risk functions for air pollution and traffic will initially be analyzed as linear and risk estimates expressed per increments to be defined when we have information on exposure contrasts within the cohorts. In the STATA script cohort-specific differences between the 5^{th} and 95^{th} percentile are used.

Sensitivity analyses

- *Extended confounder model*
  An extended confounder model (model 4) will be used in sensitivity analyses as the additional variables will not be available for all cohorts. This was also decided based upon the results of the Torino workshop where it was shown that there were no differences between effect estimates after adjustment for model 3 and model 4 for the majority of cohorts.
- *Frailty models*
  Model 3 will be used to use frailty models with the shared option in STATA. Based upon the results of the Torino workshop where it was shown that for the majority of cohorts, no random effect was found for the areas, we will ignore random effect in the main analysis. In a sensitivity analysis we will however check random effects again in all cohorts. Difficulty in fitting random effect Cox models in STATA and R contributed to this decision. If no convergence is reached in STATA an R script can be used/tried.
- *Residential stability*
  The main analysis will use the main ESCAPE exposure estimate at the baseline

address, which is available for all cohorts (except for VHM&PP; here latest address will be used). A sensitivity analysis will include only cohort participants with stable residential history. Two sensitivity analyses will be conducted (see also statistical script) using model 3:

- Model 3 restricted to subjects with at least 5 years of baseline residence (RES_5YEARS>=1 & <.)
- Model 3 restricted to subjects with no change of address during follow-up (CHANGE_AD_W6A7==0)

If you have another definition to fulfill residential stability, please communicate with the specific aim leader (Gerard Hoek).

- *Noise as additional variable*
  Noise will be included as additional confounder in the analyses for cardiovascular mortality and will be added to model 3.
- *Back-extrapolation concentrations*
  The main analysis will be based on exposure estimates taken directly from the LUR models. However we will test the sensitivity to changes in time of air pollution concentrations, backdating the LUR estimates for the baseline address to the baseline year by use of routine background monitoring data for the cohort area (see also Exposure manual, 7.1.2. Backward extrapolation of air pollution concentrations and the extended procedure about back-extrapolating in time of exposure). Model 3 will be used as confounder model.

Test of Cox proportional hazards assumption

The Cox proportional hazards assumption will be evaluated for exposure variables and potential confounders. Consequences of violation of the assumption must be decided on a case-to-case basis together with the specific aim leader, and might be stratification of statistical analyses instead of adjustment.

Effect modification

We will investigate effect modification by age, sex (sex_b), educational level (edulev_b), smoking status (smoking_b), fruit intake (fruit_b), and BMI (bmi_b). Effect modification will be analyzed in model 3 for all exposures and all endpoints. We will estimate the linear effect (with 95% CIs) of air pollutants within each stratum of the potential effect modifier. Effect modification will be tested by introduction of an interaction term between the linear air pollution variable and the potential effect modifier. If a potential effect modifier has more than 2 levels (such as smoking status), we will test for difference between all 3 levels in one test.

Fruit intake and BMI are cohort-specific due to different definitions in each cohort. The cut-off point(s) for fruit intake and BMI, however, have been identically defined for all cohorts using descriptive statistics.

Concentration response shapes

We will investigate the shape of the exposure-risk associations between each of the exposure variables and "all (cardiovascular) deaths" by visual inspection of non-linear spline plots. The plots of the exposure-risk function with 95% confidence intervals will be based on model 3. In addition to the visual inspection of the plots, we will test if these spline models fit data significantly better than linear models. Simple categorical analyses will also be performed because of the simplicity of interpretation.

Meta-analyses

Meta-analyses of linear effect estimates will be done for all combinations of all exposures and 5 endpoints and results will be presented as plots and exact quantitative estimates. Further, we will produce meta-analysis spline-plots combining the spline-functions from the different cohorts. Meta-analyses and meta-analysis spline-plots will be based on adjustment model 3.

We will test for heterogeneity between cohorts for selected combinations of exposures and endpoints. The impact of each cohort on the linear meta-analysis effect estimate will be evaluated. If heterogeneity, meta-regression models will be fitted. We will test if cohort-level variables (for example for region of Europe, study area type, mean age, prediction error of air pollution estimates, length of follow-up, and pollution mixture/elemental composition) explain possible heterogeneity.

Meta-analyses of effect modification will be conducted in addition to visual inspection of plots to assess consistency across cohorts.

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