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# Influence of short-term exposure to ultrafine and fine particles on systemic inflammation

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Abstract

Daily to monthly variations in fine particulate matter have been linked to systemic inflammatory responses. It has been hypothesized that smaller particles resulting from combustion processes confer higher toxicity. We aim to analyze the association between short-term exposure to ultrafine and fine particles and systemic inflammation. We use baseline data (2000-2003) of the Heinz Nixdorf Recall Study, a population-based cohort study of 4814 participants in the Ruhr Area in Germany. A chemistry transport model was applied to model daily surface concentrations of particulate air pollutants on a grid of 1 $km^2$. Exposure included particle number (PN) and particulate matter mass concentration with an aerodynamic diameter ≤2.5µm ($PM_{2.5}$) and ≤10µm ($PM_{10}$). Generalized additive models were used to explore the relation of air pollutants using single day lags and averaging times of up to 28 days with high-sensitivity C-reactive protein (hs-CRP). We adjusted for meteorology, season, time trend, and personal characteristics. Median hs-CRP level in the 3999 included participants was 1.5 mg/L. Median daily concentration of PN was 8,414*$10^4$/ml (IQR 4,580*$10^4$/ml), of $PM_{2.5}$ 14.5µg/m³ (IQR 11.5µg/m³) and of $PM_{10}$ 18.5µg/m³ (IQR 13.9µg/m³). A positive association between PN and hs-CRP could be observed only for single day lags and for averaged PN concentrations with higher estimates for longer averaging times. The highest hs-CRP-increase of 7.1% (95%-CI: 1.9%,12.6%) was found for the 21-day average. These results support the hypothesis that short-term exposure to traffic-related particles might lead to detrimental cardiovascular health effects via an inflammatory mechanism.

Key words: air pollution, particulate matter, inflammation, cardiovascular disease

## Introduction

Epidemiological studies on health effects of air pollution have shown adverse cardiovascular effects. Increased cardiovascular morbidity and mortality can be observed after short- and long-term exposure to particulate air pollution [1]. The biological mechanisms linking air pollution to cardiovascular events still remain mostly unclear. One possible pathway is that oxidative stress in the lungs from inhaled particulate matter (PM) leads to a systemic inflammatory cascade that can increase cardiovascular risk among susceptible individuals. The systemic inflammatory response can lead to increased coagulation ability of the blood or development and destabilization of atherosclerotic plaques [2]. Studies investigating the effect of air pollution on systemic inflammation showed inconsistent results. Some studies found associations for short-term exposure up to several days to elevated particulate air pollution levels and increased levels of inflammatory markers [3,4], whereas other studies found no association of short-term exposure and inflammatory response [5,6] or were limited to prediseased subjects [7]. Long-term exposure to particulate air pollution has been associated with an increased inflammatory response [8-10], but others did not find a consistent relationship [11].

Particulate matter is the component of air pollution which is thought to be responsible for most of the adverse effects on human health, because it contains a broad range of different toxic substances. Particles with aerodynamic diameter ≤10 µm ($PM_{10}$) and ≤2.5 µm ($PM_{2.5}$) are the most often investigated particles in the context of inflammatory markers [12]. Only few epidemiological studies concentrate also on smaller particle sizes like ultrafine particles that have an aerodynamic diameter ≤0.1µm [4, 8, 13]. Toxicological studies showed that ultrafine particles induce the greatest amount of inflammation per unit PM mass, have greater internal doses due to higher lung deposition efficiency, have enhanced oxidant capacity and

possibly are able to enter the human systemic circulation [14]. An important source of ultrafine particles is traffic exhaust, therefore ultrafine particles are regarded as a proxy for fresh traffic exposure. Ultrafine particles exhibit a strong temporal and spatial variability, because they accumulate quickly to form larger particles. Because variations in ultrafine particle concentrations are dependent on both a temporal and a spatial component it is important to provide spatially and temporally resolved exposure data. How well both kinds of variability are covered depends of the method of exposure assessment. When investigating short-term effects of ultrafine particles, day-to-day variations can be captured with central site measurements, because daily variations dependent primarily on weather conditions. To capture the spatial variability, either a very tight monitoring network needs to be applied, or the spatial distribution can be modeled with a dispersion and chemistry transport model.

Our aim was to examine short-and medium-term residential exposure to ultrafine and fine particles on systemic inflammation in a large population-based sample from an industrialized area in West Germany. We hypothesize that short-term increases in particulate air pollution at the residence of the participants are positively related to elevated high-sensitive Serum-C-reactive protein levels (hs-CRP), which is an independent predictor of cardiovascular disease [15].

## Methods

### Study design

We used baseline data from the Heinz Nixdorf Recall Study, an ongoing population-based, prospective cardiovascular cohort study that started in 2000 and includes 4,814 randomly selected participants aged 45 to 75 years from three large adjacent German cities (Essen, Mülheim, Bochum) of the densely populated and highly industrialised Ruhr Area. The study

design has been described in detail elsewhere [16]. The study was approved by the relevant institutional ethics committees and follows strict internal and external quality assurance protocols. All study participants gave informed consent prior to the examinations. The baseline assessment included a self-administered questionnaire, face to face interviews for personal risk factor assessment (i. e. family history of cardiovascular disease, hypertension, diabetes, smoking history, medications, socio-economic status), blood pressure measurements, anthropometric measurements, comprehensive laboratory tests according to standard protocols, and a multimodal assessment of subclinical atherosclerosis.

Exposure assessment

The study area covers a region of approximately 600 $km^2$. We used a residence-based approach to characterize exposure to urban air pollution. Hourly $PM_{10}$, $PM_{2.5}$, PN surface concentrations for the whole study area were estimated with the EURAD dispersion and chemistry transport model on a spatial scale of 1 km grid. The model has been described elsewhere [17, 18]. Surface concentrations were calculated by dispersing emissions in horizontal strata, taking chemical reactivity, transport processes between horizontal strata, and measured PM concentrations from state monitoring sites into account via data assimilation. That means that the primary model output is calibrated using measured PM concentrations to correct exposure concentrations in each grid cell. From the hourly values, mean daily pollutant concentrations were calculated for each 1 km² grid cell of the study area and assigned to the addresses of the participants (ArcView 9.2). Exposure data is available as 24-hour averages for each day, so the exposure of the full day was allocated to a participant even if the blood was taken in the morning. We used modelled daily exposure means of the day of each blood withdrawal (lag 0), the prior day (lag 1) up to 3 days prior to the blood withdrawal, six different moving averages ranging from 2 to 7 days and the 14-, 21- and 28-day moving average. To evaluate the characteristics of the EURAD model and the

contribution of spatial and temporal variability to the distribution of highly varying PN values at the participants addresses we compare temporal and spatial variability. Temporal variability was assessed by calculation of summary statistics for all days of a randomly chosen 1 km² and spatial variability was assessed by a randomly chosen day for all squares.

Central site daily meteorological variables (mean temperature, humidity) were obtained from the German National Meteorological Service (Deutscher Wetterdienst, DWD) for the complete study period. Season was defined as winter (1st December - 29th February), spring (1st March – 31st May), summer (1st June – 31st August) and autumn (1st September - 30th November).

Main outcome

As marker of inflammation we measured high-sensitive Serum-C-reactive protein (hs-CRP), using an automated nephelometer (BN-II, Dade-Behring Inc, Deerfield, USA). All analyses were performed in the central laboratory of the University Hospital of Essen.

Subject-related Covariates

Smoking status was defined as current smoker, ex-smoker and never-smoker. Smoking dose was assessed for current smokers with the number of smoked cigarettes per day. Cumulative smoking exposure was assessed for ex- and current smokers with the packages per day*years of smoking (packyears). Anthropometric measurements (height, weight, waist hip ratio) were conducted according to standardized protocols. Physical activity was assessed by converting daily activities and regular exercise into metabolic equivalents. Regular alcohol intake was defined as any alcohol consumption at least 4-6 days per week.

Personal characteristics, that might have an effect modifying role, were assessed as follows: Diabetes mellitus was defined by self-report or having a blood glucose ≥ 200 mg/dL or having a fasting blood glucose ≥ 126 mg/dL. Coronary heart disease (CHD) was defined as a self-reported history of a myocardial infarction or coronary intervention. Other covariates which are possible effect modifiers were sex, age (≤ 60 years, > 60 years), BMI (≤ 27 kg/m², > 27 kg/m²) and medication with HMG-CoA-reductae inhibitors (statins).

Statistical Analysis

We used a subgroup of participants with complete information on exposure, covariates and inflammatory markers. Furthermore we excluded participants with acute infections of acute exacerbations of inflammatory disease (hs-CRP > 100mg/L) from the study population (n= 4). The final analysis population consisted of 3,999 participants.

Generalized additive models were used to assess the shape of the relation between each of the exposure estimates and the hs-CRP concentration. These models allow the use of smooth functions for covariates that may not have a linear relationship with the outcome [19]. Penalized cubic regression splines were used for modelling non-linear associations [20]. Penalized splines are a nonparametric method and not sensitive to knot locations presenting an advantage if less is known of the exposure-response shape. The number of knots is chosen with an algorithm resulting in the best model fit. Besides temperature (averaged over lag 1 and 2) and time trend also continuous subject-related covariates were tested for a non-linear relation with hs-CRP. Time trend was modelled with an initial value of 12 degrees of freedom, where we assumed 4 degrees of freedom per year. For all other possible non-linear relationships, we assumed that a maximum of 3 degrees of freedom should suffice. Hs-CRP was log-transformed for two reasons, first, to obtain a symmetric distribution of regression

residuals and second, to account for an assumed exponential increase in hs-CRP for increasing exposure.

Because we are looking at short-term effects, we adjusted for temporally changing variables, namely mean temperature averaged over the 2 previous days, season and a time trend variable to represent other seasonal factors not captured by season and temperature. Subject-related covariates were based on a causal diagram which is shown elsewhere [10]. A sufficient adjustment set including time-varying variables, age, sex, city of residence and a set of lifestyle-related variables (ETS, smoking behaviour, BMI, waist-hip-ratio, alcohol intake, physical activity) was determined by using the causal diagram. In a model without exposure we identified the contributors from the lifestyle-related variable set which are significantly associated with hs-CRP and used this subset for all further models.

Effect modification of the association between the particle metrics and hs-CRP was investigated by using interaction terms for age (≤ 60, > 60 years), sex, BMI (≤ median, > median BMI), diabetes, coronary heart disease and medication with HMG-CoA-reductase inhibitors (statins).

Effect estimates from our models and their 95% confidence intervals were transformed into percent change and reported per interquartile range (IQR) of pollutants.

Sensitivity analysis

Instead of mean temperature averaged over the 2 previous days we included the temperature of the day of blood withdrawal. Furthermore, time trend and different combinations or individual-level covariates were excluded to examine the robustness of our results to different model specifications.

Analysis was performed in R 2.9.1 [21].

**Results**

The analysis population is described in table 1. Table 2 shows the descriptive statistics of the modelled pollutant concentrations. The daily mean values of $PM_{2.5}$ and $PM_{10}$ were 17.2 µg/m³ (range 183. 6 µg/m³, IQR 11.5) and 21.4 µg/m³ (range 242.2 µg/m³, IQR 13.9), respectively. $PM_{10}$ and $PM_{2.5}$ were highly correlated (Spearman correlation coefficient = 0.94) whereas PN has a low correlation with $PM_{10}$ and $PM_{2.5}$ (Spearman correlation coefficients = 0.25 and 0.21, respectively). Daily mean exposure of PN was $9{,}031*10^4$/ml (range $29{,}005*10^4$/ml, IQR $4{,}580*10^4$/ml) for the participants' residence. When comparing whether spatial or day-to-day variability contributes stronger to the variability of the participants' variability in exposure, we found a slightly higher variability in temporal exposure. The IQR of the temporal distribution of PN measured in one single square is $3{,}801*10^4$/ml (min $3{,}231*10^4$/ml, max $24{,}511*10^4$/ml) and the IQR of the spatial distribution of PN measured at a single day is $3{,}128*10^4$/ml (min $2{,}104*10^4$/ml, max $106{,}152*10^4$/ml). Hs-CRP varied between 0.1 and 84.4 mg/L with a median of 1.5 mg/L. The average of the daily mean temperature was 10.56°C (SD 7.74°C) for the whole study period.

The assessment of a possible non-linear relationship of the particle metrics with the natural logarithm of hs-CRP regression splines consistently showed curvatures below 2 degrees of freedom. This indicates a linear relationship between the different particle metrics and the natural logarithm of hs-CRP, which led us to include the exposure as a linear term in the regression model for all further analyses.

Table 3 shows the effect estimates for the association of lagged and averaged particle metrics and hs-CRP. For lag 1 evidence for a weak increase in hs-CRP of 3.22% (95%-CI: -0.97% to 7.60%) per interquartile increase in PN was observed. Hs-CRP started to increase two days after exposure to increasing levels of PN. For the moving averages this increase in hs-CRP

was more pronounced with estimates clearly above 0 and a maximum change of 7.10% (95% CI, 1.85% to 12.62%) per IQR increase in the 21-day mean PN exposure. Figure 1 shows increasing effect estimates for change in hs-CRP for longer averaging times.
For $PM_{2.5}$ and $PM_{10}$ no association with hs-CRP was seen for single day lags and moving averages up to 21 days. Only for the 28-day mean of both, $PM_{2.5}$ and $PM_{10}$, an effect was found (table 3).

Figure 2 shows results for the analysis of effect modification. Participants older than 60 years and overweight participants showed slightly higher increases in hs-CRP than younger or non-overweight participants for all averaging times. While there is some indication of effect modification due to diabetes, CHD and intake of statins, low sample sizes and wide confidence intervals do not allow definitive statements (figure 3). No effect modification between PN and hs-CRP by sex could be seen. Effect modification with $PM_{2.5}$ and with $PM_{10}$ and personal characteristics showed the same pattern as for PN, but with much lower estimates (appendix table 4). However, effect modification by statin therapy could be observed for the 28-day mean exposure of $PM_{2.5}$ and $PM_{10}$. For statin users effects are reduced to 0 whereas for non-statin users effects were found (appendix table 5).
In the sensitivity analysis the model without adjustment for trend and non-linear relationships showed the same pattern for the three exposures PN, $PM_{2.5}$ and $PM_{10}$, but slightly lower effect estimates. Other adjustment sets of personal characteristics resulted in similar exposure estimates.

**Discussion**

We found that short- and medium-term exposure to ultrafine air-borne particles is positively associated with systemic inflammation in a population-based study. Cumulative elevated levels of particle number during the 28 days before the examination were associated with an

increase in hs-CRP concentrations, independent of weather and personal characteristics. No associations of short-term exposure to $PM_{2.5}$ and $PM_{10}$ with hs-CRP could be seen. However, four weeks cumulative $PM_{2.5}$ exposure was positively associated with hs-CRP. These findings support the hypothesis that systemic inflammation is a pathway through which especially particles of smaller size can lead to an acute increase in cardiac risk.

This is the first study to use a temporally and spatially resolved exposure to assess short-term effects of ultrafine particles in a population-based study. Others used dispersion modelling to assess the long-term effect of larger particles on systemic inflammation for more highly spatially resolved data [22, 23]. Higher estimates for longer averaging times indicate perhaps a cumulative effect, but at least a smaller exposure estimation error. CRP increased as early as two days after exposure to elevated levels of PN and associations were positive up to the 28 day moving average of PN. A cross-sectional study by Zeka et al. [8] using central site measurement has shown only suggestive evidence for an association between PN exposure up to 4 weeks and hs-CRP. Different panel studies with coronary heart disease patients show positive associations between centrally measured short-term increases in PN and hs-CRP [7, 12, 22], however these studies are based on small, selected populations which are thought to be particularly vulnerable.

For $PM_{2.5}$ results from prior studies are inconsistent. In cross-sectional analyses of population-based studies, Diez-Roux et al. [5] and Zeka et al. [8] found no consistent evidence that recent exposure to $PM_{2.5}$ is associated with hs-CRP. However, weak associations for longer averaging times were found [5]. Similarly, we found associations of longer averaging times of $PM_{2.5}$ with hs-CRP. In this study, the 28 day moving average was associated with CRP and in a prior study we showed that the long-term PM2.5 exposure at the home address was associated with increases in CRP and fibrinogen [10]. No associations of short-term exposure

to $PM_{2.5}$ and $PM_{10}$ with hs-CRP could be seen. In contrast, in a panel study of older participants, short-term increases in $PM_{2.5}$ were associated with hs-CRP levels [25]. Chuang et al. [24], Rückerl et al. [7] and Seaton et al. [27] found evidence for a short-term increase of $PM_{10}$ and elevated hs-CRP levels. Overall, studies suggest association between air pollution and inflammation. The heterogeneity present in study results can be due to different pollution mixtures, methods of exposure assessment, study design, or caused by different susceptibilities of the populations under study, based on underlying medical conditions or treatments with anti-inflammatory effect.

Another important factor for differences between studies could be the study design. Unlike in a panel study where repeated measures on the same individual makes confounding by personal variables unlikely, in a cross-sectional analysis confounding by personal characteristics must be taken in account. Depending on the appropriate choice of confounders in a cross-sectional analysis the association between exposure and outcome could be biased. We chose the model with the help of causal diagrams which are strongly dependent on assumptions regarding the temporal and causal relations between variables. These relations are based on prior knowledge. However other causal relations could be possible, resulting in another choice of adjustment variables. Therefore, we investigated the robustness of our results to different model specifications, but did not find qualitative changes in our results.

The different sizes and types of inhaled pollutants may determine the importance of different biological pathways. These pathways are not entirely exclusive and may overlap temporally or be activated at different time points after exposure [1]. Ultrafine particles or soluble constituents of PM can directly enter the blood stream and cause primary a systemic inflammation. Larger particles cannot be transported into the circulation, but might induce a secondary pro-inflammatory response by first producing a local inflammation in the lung.

Primary inflammation produces more acute response to particles and an increase in acute-phase reactants that can be seen after one to a few days, whereas it is possible that pulmonary tissue oxidative stress induced by larger particles is activated after a longer period of constant enhanced exposure [1].

Particle number and mass display a different spatio-temporal pattern. PN is mainly dominated by ultrafine particles because they occur in a large number. Ultrafine particles are generated by traffic and are very unstable. The concentration of ultrafine particles decreases rapidly perpendicular to highly trafficked roads and reaches background concentrations within 300 m [28]. The 1 km² resolution of the EURAD model, however, estimates only the average PN concentration within this 1 km² grid cell. Pollution peaks close to busy roads will therefore not be captured. $PM_{2.5}$ and $PM_{10}$ display a more homogeneous spatial distribution. Larger particles are more evenly dispersed because they are more stable and stem from a variety of sources other than motorized traffic in this area (industry, coal combustion, agriculture, sea salt) and long range transport mechanisms [29].

Compared to larger particles it is expected that ultrafine particles are controlled to a larger extent by meteorological parameters as wind speed and temperature. This might lead in general to a stronger day-to-day variability of PN compared to PM2.5 and PM10. We examined whether the spatial or temporal variability dominates the short-term exposure pattern of ultrafine particles in our region. With the use of the EURAD model we were able to investigate both spatial and temporal variability of the PN background concentration, because exposure was modeled for each participants' home address and for every day of the study period. We expected that the spatial variability of PN to be lower because the 1km² grid cell average of the PN concentration does not capture the true concentration differences within our

study population. On the other hand, day-to-day variability based on meteorological data should be larger, because the temporal variability can be modelled with a greater degree of precision based on hourly meteorological data. When comparing spatial variability of a randomly chosen day and day-to-day variability of a randomly chosen square we found a slightly higher temporal variability as measured with the IQR.

Suggestive evidence for effect modification of the association between PN and hs-CRP by different personal characteristics could be observed. We found that older (> 60 years) and overweight persons (BMI > 27 kg/m³) are more affected by elevated ultrafine pollution. Also participants with CHD showed higher responses to increased air pollution levels suggesting that participants with conditions that increase their cardiovascular risk are more vulnerable to the effect of small particle air pollution. Participants on statin therapy showed no increase in hs-CRP levels with higher air pollution probably due to the anti-inflammatory property of the drug. This was also observed in previous research [13, 24]. Sex-specific effects of air pollution with inflammatory markers have been reported by others, but were not observed in our analysis [6, 10]. However, in our study population, sex differences in the association of hs-CRP and coronary artery disease have been documented [30].

A limitation of the study is the possibility of exposure misclassification in this residence-based approach of short-term exposure estimation. It is not known, whether the participants actually stayed close to their home address during the days prior to the blood draw. Therefore we are not able to correct for exposures in other environments like the work environment or individual traffic exposure. Strength of the study includes the high degree of spatial resolution within our study area in comparison to central site measurements. This enables a more exact exposure assessment at the home address.

In conclusion, our results indicate an immediate response of hs-CRP to ambient air pollution of ultrafine particles. This supports the hypothesis that short-term exposure to traffic-related particles might lead to detrimental cardiovascular health effects via an inflammatory mechanism.

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Table legends:

Tab 1. Descriptive statistics of the study population (n=3,999)

Tab 2. Summary statistics of hs-CRP, meteorological variables and air pollution concentrations for participants' residence on the day of blood draw (including also spatial and temporal distribution of PN)

Tab 3. Adjusted* estimates for percent change of hs-CRP per IQR of PN, $PM_{2.5}$ and $PM_{10}$ *for sex, age, smoking habits, BMI, waist-hip ratio, alcohol intake, physical activity, temperature, time trend, season and city

Appendix tables

Tab 4. Adjusted estimates* for effect modifications of association between PN, $PM_{2.5}$ and $PM_{10}$ and hs-CRP stratified by personal characteristics (sex, age, BMI)

Tab 5. Adjusted estimates* for effect modifications of association between PN, $PM_{2.5}$ and $PM_{10}$ and hs-CRP stratified by medical conditions (diabetes, CHD, statine intake)

Figure legends:

Fig 1. Adjusted estimates for percent change of hs-CRP for different exposure periods of PN

IQR=Interquartile Range

Fig 2. Effect modification of association between PN (exposure averaged over 2 to 28 days) and hs-CRP by personal characteristics

IQR=Interquartile Range

Fig 3. Effect modification of association between PN (exposure averaged over 2 to 28 days) and hs-CRP by medical condition

IQR=Interquartile Range
CHD=Coronary Heart Disease

| | Total (n=3,999) | Men (n=2,014) | Women (n=1,985) |
|---|---|---|---|
| Age (mean ± SD[c]) | 59 ± 7.7 | 59.6 ± 7.7 | 59.3 ± 7.8 |
| BMI kg/m² (mean ± SD[c]) | 27.9 ± 4.6 | 28.2 ± 3.9 | 27.7 ± 5.2 |
| Waist-Hip-Ratio (mean ± SD[c]) | 0.91 ± 0.09 | 0.97 ± 0.06 | 0.85 ± 0.07 |
| City (%) | | | |
| Mülheim | 37.3 | 37.5 | 37.0 |
| Essen | 33.1 | 32.3 | 34.0 |
| Bochum | 29.6 | 30.2 | 29.0 |
| Smoking status (%) | | | |
| Smoker | 23.1 | 24.6 | 21.5 |
| Ex-smoker | 35.4 | 47.3 | 23.4 |
| Never smoker | 41.5 | 28.1 | 55.2 |
| ETS[a] (%) | 32.4 | 34.2 | |
| Diabetes (%) | 13.7 | 34.2 | 9.5 |
| CHD[b] (%) | 6.7 | 10.7 | 2.7 |
| Statin intake (%) | 10.6 | 13.01 | 8.06 |
| Regular alcohol intake (%) | 20.4 | 30.00 | 10.6 |

[a]Environmental Tobacco Smoke
[b]Coronary Heart Disease
[c]Standard Deviation

| Variable | Mean | SD[a] | Min | 1th quartile | Median | 3th quartile | Max | IQR[b] | N |
|---|---|---|---|---|---|---|---|---|---|
| Mean daily Temperature (°C) | 10.56 | 7.74 | -11.23 | 5.22 | 10.89 | 16.39 | 29.23 | 11.17 | 3,999 |
| Mean daily humidity (g/kg) | 6.5 | 2.6 | 1.3 | 4.6 | 6.2 | 8.3 | 14.2 | 3.7 | 3,999 |
| $PM_{2.5}$ (µg/m³) | 17.23 | 10.81 | 3.54 | 10.12 | 14.55 | 21.61 | 187.10 | 11.50 | 3,999 |
| $PM_{10}$ (µg/m³) | 21.44 | 12.85 | 3.82 | 12.84 | 18.45 | 26.74 | 246.00 | 13.90 | 3,999 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PN (*$10^4$/ml) | 9,031 | 3,697 | 2,085 | 6,408 | 8,414 | 10,980 | 31,090 | 4,580 | 3,999 |
| Spatial dist. of PN (*$10^4$/ml) | 6,925 | 7,022 | 2,104 | 4,132 | 5,240 | 7,260 | 106,152 | 3,128 | 1,326 |
| Temporal dist. of PN (*$10^4$/ml) | 9,630 | 3,167 | 3,231 | 7,450 | 9,028 | 11,251 | 24,511 | 3,801 | 1,185 |
| Hs-CRP (mg/L) | 3.0 | 5.2 | 0.1 | 0.7 | 1.5 | 3.2 | 84.4 | 2.5 | 3,999 |

[a]Standard Deviation
[b]Interquartile Range

| | | PN | | $PM_{2.5}$ | | $PM_{10}$ | |
|---|---|---|---|---|---|---|---|
| | | % change | 95% CI[a] | % change | 95% CI[a] | % change | 95% CI[a] |
| Single day lags | 0 | -0.33 | -4.48, 4.00 | 1.66 | -1.82, 5.26 | 0.85 | -2.66, 4.49 |
| | 1 | 3.22 | -0.97, 7.60 | 0.74 | -2.64, 4.24 | -0.02 | -3.52, 3.62 |
| | 2 | 4.23 | 0.04, 8.60 | 1.03 | -2.85, 5.06 | 0.97 | -2.90, 4.98 |
| | 3 | 2.47 | -1.64, 6.74 | 2.03 | -1.67, 5.87 | 1.34 | -2.36, 5.17 |
| Moving averages | 2 | 4.49 | 0.04, 9.12 | 1.00 | -2.66, 4.80 | 0.51 | -3.28, 4.46 |
| | 3 | 4.42 | -0.07, 9.11 | 1.57 | -2.13, 5.42 | 0.95 | -2.89, 4.95 |
| | 4 | 4.81 | 0.20, 9.62 | 0.70 | -3.17, 4.71 | 0.21 | -3.72, 4.30 |
| | 5 | 5.53 | 0.74, 10.54 | 0.23 | -3.84, 4.47 | -0.18 | -4.27, 4.08 |
| | 6 | 5.86 | 1.06, 10.89 | -0.10 | -4.25, 4.22 | -0.41 | -4.62, 3.98 |
| | 7 | 5.54 | 0.68, 10.63 | -0.72 | -4.67, 3.39 | -1.28 | -5.45, 3.07 |
| | 14 | 6.64 | 1.60, 11.93 | 0.05 | -4.06, 4.33 | -0.90 | -5.20, 3.60 |
| | 21 | 7.10 | 1.85, 12.62 | 2.17 | -2.65, 7.22 | 1.13 | -3.86, 6.38 |
| | 28 | 6.38 | 1.08, 11.96 | 7.06 | 1.42, 13.02 | 5.16 | -0.41, 11.04 |

[a]Confidence Interval

| | | | PN | | $PM_{2.5}$ | | $PM_{10}$ |
|---|---|---|---|---|---|---|---|
| | Moving average | % change | 95% CI[a] | % change | 95% CI[a] | % change | 95% CI[a] |
| Men (n=2,014) | 2 | 3.70 | -2.12, 9.87 | 1.17 | -3.70,6.29 | 1.02 | -4.03,6.34 |
| | 3 | 4.31 | -1.62, 10.61 | 1.74 | -3.23,6.97 | 1.77 | -3.38,7.19 |
| | 4 | 4.66 | -1.43, 11.12 | 1.76 | -3.46,7.27 | 1.96 | -3.33,7.54 |
| | 5 | 5.14 | -1.10, 11.78 | 1.09 | -4.35,6.85 | 1.48 | -3.96,7.23 |
| | 6 | 5.63 | -0.61, 12.25 | 1.10 | -4.40,6.92 | 1.51 | -4.07,7.41 |
| | 7 | 5.61 | -0.69, 12.30 | 0.94 | -4.35,6.51 | 0.99 | -4.56,6.87 |
| | 14 | 7.56 | 1.07, 14.47 | 0.82 | -4.53,6.48 | 0.27 | -5.28,6.15 |
| | 21 | 7.40 | 0.71, 14.53 | 1.82 | -4.25,8.27 | 1.07 | -5.18,7.74 |
| | 28 | 6.64 | -0.08, 13.81 | 7.84 | 0.79,15.39 | 6.08 | -0.88,13.52 |
| Women (n=1,985) | 2 | 5.27 | -0.64, 11.54 | 0.81 | -4.31,6.20 | -0.04 | -5.28,5.48 |
| | 3 | 4.52 | -1.31, 10.70 | 1.40 | -3.70,6.77 | 0.09 | -5.14,5.60 |
| | 4 | 4.95 | -1.00, 11.25 | -0.42 | -5.66,5.11 | -1.64 | -6.93,3.94 |
| | 5 | 5.90 | -0.32, 12.52 | -0.70 | -6.23,5.17 | -1.99 | -7.49,3.83 |
| | 6 | 6.09 | -0.14, 12.71 | -1.43 | -7.07,4.55 | -2.56 | -8.23,3.46 |
| | 7 | 5.46 | -0.80, 12.12 | -2.51 | -7.83,3.11 | -3.78 | -9.34,2.13 |
| | 14 | 5.70 | -0.74, 12.56 | -0.81 | -6.31,5.02 | -2.22 | -7.93,3.85 |
| | 21 | 6.79 | 0.04, 14.00 | 2.54 | -3.76,9.25 | 1.19 | -5.24,8.06 |
| | 28 | 6.10 | -0.73, 13.40 | 6.25 | -0.81,3.81 | 4.20 | -2.75,11.65 |
| Age <= 60 years (n=2,123) | 2 | 2.46 | -3.10, 8.35 | -0.65 | -5.22,4.14 | -0.67 | -5,37,4,25 |
| | 3 | 2.28 | -3.35, 8.23 | -0.33 | -4.96,4.53 | -0.85 | -5,58,4,11 |
| | 4 | 2.12 | -3.58, 8.16 | -1.64 | -6.45,3.41 | -2.11 | -6,92,2,95 |
| | 5 | 2.54 | -3.38, 8.83 | -2.95 | -7.96,2.34 | -3.08 | -8,04,2,15 |
| | 6 | 2.55 | -3.38, 8.85 | -3.99 | -9.11,1.43 | -4.06 | -9,19,1,36 |
| | 7 | 2.10 | -3.87, 8.45 | -4.64 | -9.59,0.59 | -5.05 | -10,17,0,37 |
| | 14 | 4.21 | -2.08, 10.90 | -3.68 | -8.79,1.72 | -4.07 | -9,31,1,47 |
| | 21 | 5.10 | -1.46, 12.09 | -1.19 | -7.08,5.08 | -1.47 | -7,49,4,94 |
| | 28 | 4.03 | -2.55, 11.05 | 5.37 | -1.44,12.66 | 3.71 | -2,94,10,82 |
| Age > 60 years (n=1,876) | 2 | 6.47 | 0.28, 13.05 | 3.42 | -2.15,9.30 | 2.52 | -3.27,8.65 |
| | 3 | 6.34 | 0.20, 12.86 | 4.32 | -1.27,10.23 | 3.90 | -1.95,10.10 |
| | 4 | 7.39 | 1.05, 14.12 | 4.12 | -1.70,10.29 | 3.87 | -2.11,10.21 |
| | 5 | 8.33 | 1.78, 15.30 | 4.88 | -1.27,11.41 | 4.48 | -1.75,11.10 |
| | 6 | 9.08 | 2.54, 16.03 | 5.23 | -0.94,11.78 | 5.00 | -1.32,11.72 |
| | 7 | 9.04 | 2.44, 16.07 | 4.23 | -1.51,10.31 | 3.98 | -2.18,10.53 |
| | 14 | 9.12 | 2.47, 16.20 | 4.78 | -1.06,10.97 | 3.56 | -2.61,10.12 |
| | 21 | 9.32 | 2.41, 16.69 | 6.29 | -0.25,13.25 | 4.65 | -2.11,11.88 |
| | 28 | 9.13 | 2.13, 16.61 | 9.47 | 2.09,17.37 | 7.54 | 0.17,15.45 |
| BMI <=27 kg/m² (n=1,857) | 2 | 2,45 | -3.53,8.79 | -1.92 | -6.88.3.32 | -2.84 | -7.95,2.55 |
| | 3 | 1.60 | -4.27,7.83 | -1.86 | -6.85.3.40 | -3.08 | -8.21,2.33 |
| | 4 | 1.62 | -4.35,7.97 | -2.91 | -8.13.2.60 | -4.01 | -9.24,1.51 |
| | 5 | 2.63 | -3.59,9.25 | -2.98 | -8.52.2.90 | -3.80 | -9.26,1.99 |
| | 6 | 2.87 | -3.34,9.48 | -3.93 | -9.54.2.02 | -4.85 | -10.42,1.08 |
| | 7 | 2.68 | -3.59,9.37 | -4.82 | -10.17.0.84 | -6.00 | -11.50,-0.16 |
| | 14 | 3.59 | -2.96,10.59 | -2.72 | -8.21.3.11 | -4.83 | -10.44,1.12 |
| | 21 | 3.62 | -3.24,10.97 | 0.10 | -6.15.6.78 | -2.62 | -8.95,4.14 |
| | 28 | 2.47 | -4.41,9.84 | 4.64 | -2.45.12.25 | 1.17 | -5.75,8.60 |
| BMI >27 kg/m² (n=2,142) | 2 | 7.52 | 1.69,13.69 | 4.46 | -0.58.9.76 | 4.32 | -0.88,9.80 |
| | 3 | 7.90 | 1.96,14.18 | 5.09 | 0.00.10.44 | 5.08 | -0.18,10.62 |
| | 4 | 8.73 | 2.64.15.19 | 4.57 | -0.69.10.12 | 4.90 | -0.48,10.58 |
| | 5 | 9.26 | 2.96.15.94 | 3.57 | -1.89,9.34 | 3.94 | -1.58,9.77 |
| | 6 | 9.83 | 3.52.16.53 | 3.40 | -2.13,9.25 | 4.02 | -1.66,10.03 |
| | 7 | 9.46 | 3.11.16.19 | 2.57 | -2.67,8.09 | 3.05 | -2.57,8.99 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 14 | 10.32 | 3.88.17.16 | 2.41 | -2.96,8.07 | 2.86 | -2.81,8.86 |
| | 21 | 11.11 | 4.46.18.19 | 3.65 | -2.45,10.13 | 4.51 | -1.85,11.29 |
| | 28 | 10.73 | 4.00.17.89 | 8.66 | 1.64,16.16 | 8.42 | 1.44,15.89 |
| Moving | | | | | | | |

PM2.5

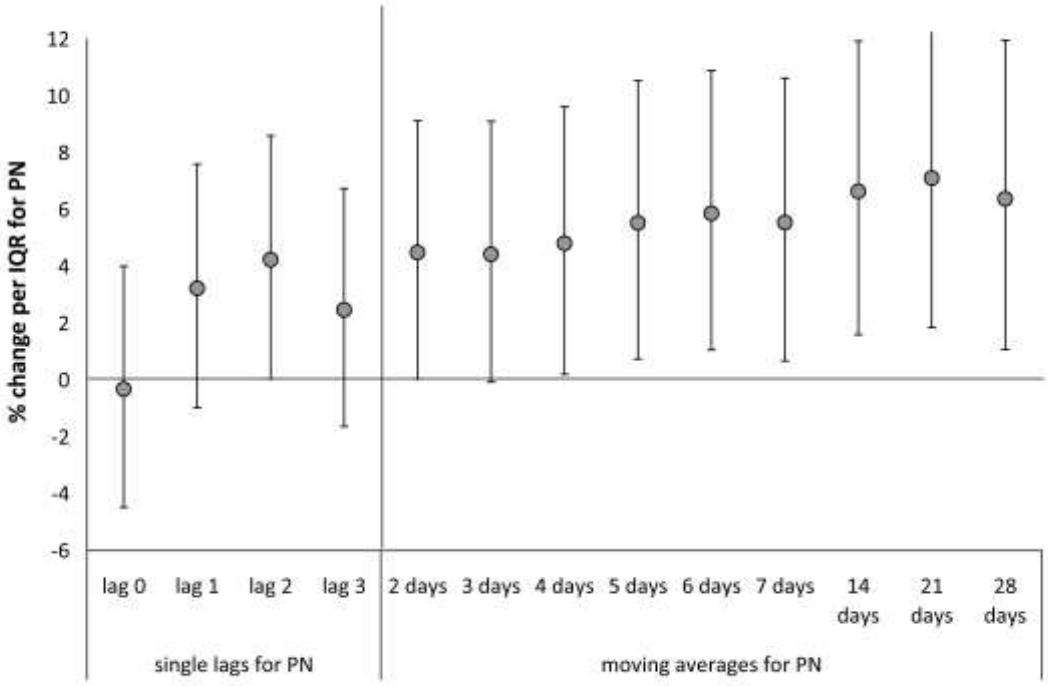
PM10

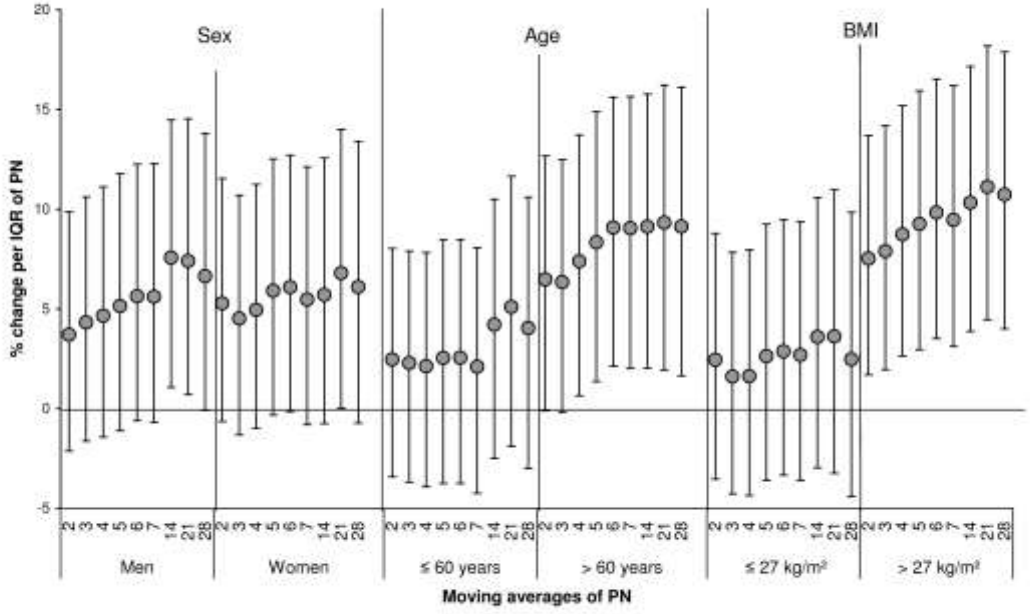
*for sex, age, smoking habits, BMI, waist-hip ratio, alcohol intake, physical activity, temperature, time trend, season and city

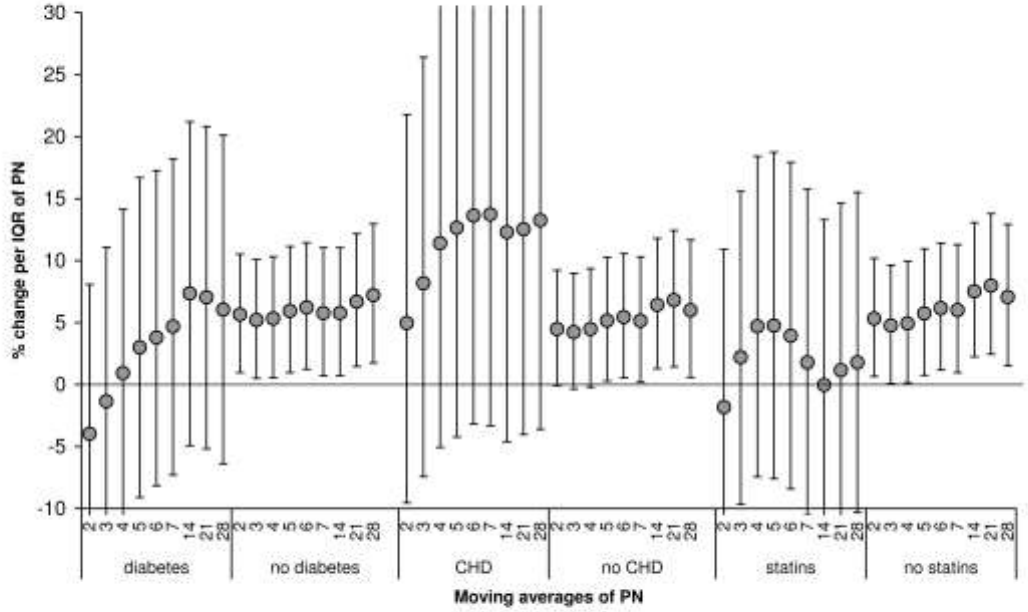
[a]Confidence Interval

| | average | change | | change | | change | |
|---|---|---|---|---|---|---|---|
| Diabetes | 2 | -3.97 | -14.69,8.09 | 0.65 | -9.02,11.34 | -1.96 | -11.63,8.76 |
| (n=549) | 3 | -1.37 | -12.40,11.05 | 0.93 | -8.48,11.32 | -1.03 | -10.56,9.52 |
| | 4 | 0.92 | -10.77,14.13 | -0.77 | -10.11,9.55 | -2.59 | -11.98,7.79 |
| | 5 | 2.99 | -9.10,16.69 | -1.82 | -11.31,8.67 | -3.30 | -12.81,7.25 |
| | 6 | 3.78 | -8.15,17.27 | -2.26 | -11.78,8.27 | -3.56 | -13.26,7.23 |
| | 7 | 4.68 | -7.29,18.19 | -3.08 | -12.44,7.27 | -4.77 | -14.60,6.20 |
| | 14 | 7.34 | -4.92,21.19 | -6.12 | -15.65,4.50 | -7.83 | -17.54,3.01 |
| | 21 | 7.03 | -5.19,20.82 | -6.43 | -16.93,5.39 | -7.01 | -17.69,5.06 |
| | 28 | 6.04 | -6.39,20.11 | -1.14 | -12.85,12.14 | -2.61 | -14.09,10.41 |
| No | 2 | 5.63 | 0.96,10.51 | 1.09 | -2.77,5.10 | 0.92 | -3.09,5.09 |
| diabetes | 3 | 5.18 | 0.50,10.09 | 1.68 | -2.24,5.76 | 1.28 | -2.79,5.52 |
| (n=3450) | 4 | 5.32 | 0.54,10.32 | 0.94 | -3.17,5.23 | 0.68 | -3.50,5.05 |
| | 5 | 5.93 | 0.97,11.13 | 0.58 | -3.77,5.12 | 0.35 | -4.01,4.90 |
| | 6 | 6.22 | 1.23,11.45 | 0.28 | -4.15,4.92 | 0.13 | -4.36,4.84 |
| | 7 | 5.76 | 0.72,11.05 | -0.30 | -4.50,4.08 | -0.69 | -5.12,3.94 |
| | 14 | 5.76 | 0.72,11.05 | -0.30 | -4.50,4.08 | -0.69 | -5.12,3.94 |
| | 21 | 6.68 | 1.46,12.17 | 1.01 | -3.32,5.54 | 0.26 | -4.29,5.04 |
| | 28 | 7.21 | 1.75,12.96 | 3.43 | -1.60,8.71 | 2.35 | -2.85,7.83 |
| CHD[b] | 2 | 4.95 | -9.54,21.77 | 5.61 | -7.58,20.69 | 5.06 | -8.04,20.03 |
| (n=269) | 3 | 8.17 | -7.43,26.39 | 7.72 | -5.75,23.12 | 6.71 | -6.85,22.25 |
| | 4 | 11.39 | -5.07,30.70 | 7.95 | -5.93,23.88 | 7.06 | -6.79,22.97 |
| | 5 | 12.63 | -4.23,32.45 | 3.92 | -9.63,19.50 | 3.26 | -10.24,18.79 |
| | 6 | 13.61 | -3.15,33.28 | 4.33 | -9.42,20.16 | 4.93 | -9.07,21.09 |
| | 7 | 13.71 | -3.32,33.74 | 3.64 | -9.70,18.96 | 2.73 | -10.97,18.54 |
| | 14 | 12.28 | -4.61,32.16 | 5.41 | -8.52,21.47 | 3.77 | -9.91,19.52 |
| | 21 | 12.52 | -4.03,31.93 | -1.91 | -15.87,14.37 | -3.87 | -17.70,12.29 |
| | 28 | 13.24 | -3.60,33.04 | 2.25 | -13.24,20.50 | 0.54 | -14.78,18.61 |
| No CHD[b] | 2 | 4.47 | -0.08,9.22 | 0.65 | -3.09,4.53 | 0.12 | -3.76,4.16 |
| (n=3,730) | 3 | 4.21 | -0.36,8.99 | 1.09 | -2.69,5.01 | 0.47 | -3.45,4.54 |
| | 4 | 4.47 | -0.20,9.36 | 0.10 | -3.83,4.20 | -0.39 | -4.39,3.78 |
| | 5 | 5.15 | 0.29,10.25 | -0.17 | -4.33,4.17 | -0.58 | -4.75,3.78 |
| | 6 | 5.44 | 0.56,10.56 | -0.56 | -4.79,3.86 | -0.96 | -5.26,3.53 |
| | 7 | 5.13 | 0.19,10.31 | -1.13 | -5.16,3.06 | -1.71 | -5.97,2.74 |
| | 14 | 6.41 | 1.27,11.80 | -0.37 | -4.54,3.97 | -1.36 | -5.73,3.22 |
| | 21 | 6.80 | 1.44,12.44 | 2.41 | -2.47,7.53 | 1.45 | -3.63,6.78 |
| | 28 | 5.98 | 0.58,11.67 | 7.39 | 1.72,13.37 | 5.45 | -0.18,11.39 |
| Statins | 2 | -1.84 | -13.13,10.91 | -3.50 | -13.86,8.11 | -4.61 | -15.01,7.07 |
| intake | 3 | 2.19 | -9.64,15.57 | -3.94 | -14.31,7.69 | -4.84 | -15.24,6.83 |
| (n=422) | 4 | 4.69 | -7.44,18.41 | -4.96 | -15.51,6.91 | -5.68 | -16.00,5.91 |
| | 5 | 4.75 | -7.60,18.75 | -5.73 | -16.54,6.47 | -6.50 | -17.02,5.36 |
| | 6 | 3.92 | -8.42,17.92 | -6.11 | -17.05,6.26 | -6.51 | -17.25,5.63 |
| | 7 | 1.77 | -10.52,15.75 | -6.78 | -17.27,5.03 | -7.42 | -18.02,4.55 |
| | 14 | -0.04 | -11.80,13.30 | 0.30 | -11.03,13.06 | -0.61 | -11.61,11.75 |
| | 21 | 1.14 | -10.76,14.62 | -0.17 | -12.02,13.27 | -0.56 | -12.17,12.59 |
| | 28 | 1.77 | -10.33,15.50 | 1.00 | -11.68,15.50 | 1.28 | -10.93,15.16 |
| No statins | 2 | 5.31 | 0.66,10.18 | 1.49 | -2.34,5.47 | 1.07 | -2.90,5.20 |
| intake | 3 | 4.75 | 0.09,9.64 | 2.12 | -1.75,6.15 | 1.59 | -2.43,5.77 |
| (n=3,577) | 4 | 4.92 | 0.14,9.93 | 1.30 | -2.74,5.51 | 0.93 | -3.19,5.23 |
| | 5 | 5.73 | 0.75,10.96 | 0.93 | -3.34,5.37 | 0.63 | -3.65,5.11 |
| | 6 | 6.15 | 1.17,11.39 | 0.60 | -3.74,5.13 | 0.40 | -4.01,5.02 |
| | 7 | 6.00 | 0.95,11.30 | -0.06 | -4.19,4.24 | -0.49 | -4.86,4.08 |
| | 14 | 7.51 | 2.24,13.06 | -0.03 | -4.26,4.39 | -0.87 | -5.34,3.80 |
| | 21 | 7.97 | 2.45,13.79 | 2.55 | -2.40,7.76 | 1.58 | -3.59,7.02 |
| | 28 | 7.06 | 1.50,12.92 | 7.98 | 2.20,14.09 | 5.96 | 0.19,12.05 |

*for sex, age, smoking habits, BMI, waist-hip ratio, alcohol intake, physical activity, temperature, time trend, season and city
[a] Confidence Interval
[b] Coronary Heart Disease




% change per IQR of PN
30
25
20
15
10
5
0
-5
-10
2 3 4 5 6 7 14 21 28
diabetes
no diabetes
CHD
no CHD
statins
no statins
Moving averages of PN