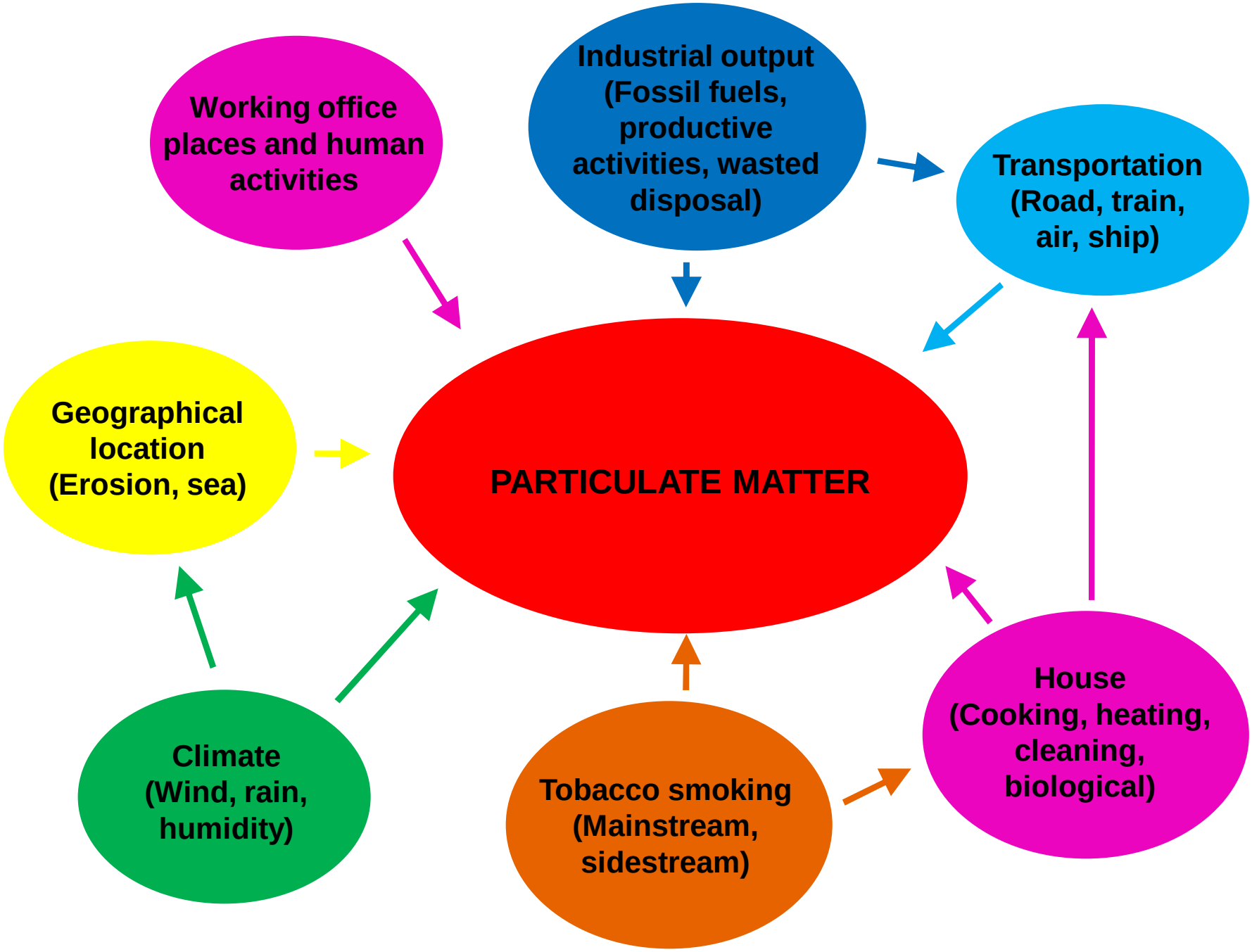

**PROGETTO INTERDIPARTIMENTALE AMBIENTE E SALUTE:**

***Workshop, Roma 18 Giugno 2009***

# STATO DI AVANZAMENTO E PROSPETTIVE

## GPF2 – Polveri e effetti cardiopolmonari: progetto di fattibilità

**Fabio Cibella, Sandra Baldacci, Sara Maio, Giovanni Viegi**
**IBIM-CNR, Palermo, and IFC-CNR, Pisa**


Possible sources of PM

# Potential Role of Ultrafine Particles in Associations between Airborne Particle Mass and Cardiovascular Health

*Ralph J. Delfino,[1] Constantinos Sioutas,[2] and Shaista Malik[3]*

VOLUME 113 | NUMBER 8 | August 2005 • Environmental Health Perspectives

Numerous epidemiologic time-series studies have shown generally consistent associations of cardiovascular hospital admissions and mortality with outdoor air pollution, particularly mass concentrations of particulate matter (PM) ≤ 2.5 or ≤ 10 μm in diameter ($PM_{2.5}$, $PM_{10}$). Panel studies with repeated measures have supported the time-series results showing associations between PM and risk of cardiac ischemia and arrhythmias, increased blood pressure, decreased heart rate variability, and increased circulating markers of inflammation and thrombosis. The causal components driving the PM associations remain to be identified. Epidemiologic data using pollutant gases and particle characteristics such as particle number concentration and elemental carbon have provided indirect evidence that products of fossil fuel combustion are important. Ultrafine particles < 0.1 μm (UFPs) dominate particle number concentrations and surface area and are therefore capable of carrying large concentrations of adsorbed or condensed toxic air pollutants. It is likely that redox-active components in UFPs from fossil fuel combustion reach cardiovascular target sites. High UFP exposures may lead to systemic inflammation through oxidative stress responses to reactive oxygen species and thereby promote the progression of atherosclerosis and precipitate acute cardiovascular responses ranging from increased blood pressure to myocardial infarction. The next steps in epidemiologic research are to identify more clearly the putative PM casual components and size fractions linked to their sources. To advance this, we discuss in a companion article (*Sioutas C, Delfino RJ, Singh M. 2005. Environ Health Perspect 113:947-955*) the need for and methods of UFP exposure assessment

**Delfino, Envir Health Perspect 2005**

# Adverse cardiovascular effects of air pollution

Nicholas L Mills*, Ken Donaldson, Paddy W Hadoke, Nicholas A Boon, William MacNee, Flemming R Cassee, Thomas Sandström, Anders Blomberg and David E Newby

NATURE CLINICAL PRACTICE JANUARY 2009 VOL 6 NO 1

Air pollution is increasingly recognized as an important and modifiable determinant of cardiovascular disease in urban communities. exposure has been linked to a range of including and heart failure. exposure increases an individual's lifetime The of these adverse health effects seems to be that incorporate reactive organic and transition metal components. Inhalation of this particulate matter leads to with secondary systemic effects or, after translocation from the lung into the circulation, to Through the induction of cellular oxidative stress and proinflammatory pathways, particulate matter augments the development and progression of atherosclerosis via detrimental effects on platelets, vascular tissue, and the myocardium. These effects seem to underpin the atherothrombotic consequences of acute and chronic exposure to air pollution. An increased understanding of the mediators and mechanisms of these processes is necessary if we are to develop strategies to protect individuals at risk and reduce the effect of air pollution on cardiovascular disease.

**Mills, Nature Clinical Practice 2009**

# Indoor ultrafine particles and childhood asthma: exploring a potential public health concern

**S. Weichenthal, A. Dufresne, C. Infante-Rivard**

*Indoor Air 2007; 17: 81–91*

**Abstract** Exposure to airborne particulate matter has a negative effect on respiratory health in both children and adults. The [redacted] air pollution is of particular interest because of its increased ability to cause [redacted]. We reviewed the literature, and to date findings suggest that ultrafine particles (UFPs) may play an important role [redacted]. Furthermore, we believe that indoor UFP exposures may be particularly important because people spend the majority of their time indoors where sources of these contaminants are often present. While several epidemiological studies have examined the respiratory effects of ambient UFP exposures, the relationship between indoor UFP exposures and childhood asthma has yet to be examined in clinical or epidemiological studies. However, the portable instrumentation necessary to conduct such investigations is increasingly available, and we expect that this issue will be addressed in the near future. Therefore, the aim of this article is to provide a general review of UFP toxicity as related to childhood asthma in order to draw attention to a potentially important public health concern.

**Weichenthal et al, Indoor Air 2007**

# Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark

Z J Andersen, P Wahlin, O Raaschou-Nielsen, M Ketzel, T Scheike and S Loft

*Occup. Environ. Med.* 2008;65;458-466; originally published online 7 Nov 2007;

OBJECTIVES: To study the association between short-term exposure to ultrafine particles and morbidity in Copenhagen, Denmark

METHODS: We studied the association between urban background levels of the total number concentration of particles ($NC_{tot}$, 6-700 nm in diameter) measured at a single site (15 May 2001 to 31 December 2004) and hospital admissions due to cardiovascular (CVD) and respiratory disease (RD) in the elderly (age ≥ 65 years), and due to asthma in children (age 5-18 years). We examined these associations in the presence of $PM_{10}$, $PM_{2.5}$ (particulate matter <10 and 2.5 μm in diameter, respectively) and ambient gasses. We utilised data on size distribution to calculate $NC_{tot}$ for four modes with median diameters 12, 23, 57 and 212 nm, and $NC_{100}$ (number concentration of particles <100 nm in diameter) and examined their associations with health outcomes. We used a time series Poisson generalised additive model adjusted for overdispersion, season, day of the week, public holidays, school holidays, influenza, pollen and meteorology, with up to 5 days' lagged exposure

RESULTS AND CONCLUSIONS: The adverse health effects of particulate matter on CVD and RD hospital admissions in the elderly were mainly mediated by $PM_{10}$ and accumulation mode particles with lack of effects for $NC_{100}$. For paediatric asthma, accumulation mode particles, $NC_{100}$ and nitrogen oxides (mainly from traffic related sources) were relevant, whereas $PM_{10}$ appeared to have little effect. Our results suggest that particle volume/mass from long-range transported air pollution is relevant for CVD and RD admissions in the elderly, and possibly particle numbers from traffic sources for paediatric asthma

**Andersen et al, Occup Environ Med 2008**

# Effect of Particulate Air Pollution on Lung Function in Adult and Pediatric Subjects in a Seattle Panel Study*

Carol A. Trenga, Jeffrey H. Sullivan, Jonathan S. Schildcrout, Kristen P. Shepherd, Gail G. Shapiro, L.-J. Sally Liu, Joel D. Kaufman and Jane Q. Koenig

*Chest* 2006;129;1614-1622

*Study objective:* To determine whether [redacted] (PM), [redacted] was associated with [redacted].
*Participants:* We studied 37 [redacted] and 17 [redacted] with physician-diagnosed [redacted] in Seattle during a 3-year [redacted].
*Study design and measurements:* Indoor and outdoor PM measurements were made at subjects' homes. The subjects wore personal exposure monitors for 10 consecutive 24-h periods, and PM was also measured at a central outdoor location. We assessed the within-subject effect of particulate exposure on $FEV_1$ and peak expiratory flow (PEF) in adults, and maximal midexpiratory flow (MMEF), PEF, $FEV_1$, and symptoms in children.
*Results:* $FEV_1$ decrements were associated with 1-day lagged central site PM ≤ 2.5 μm in diameter ($PM_{2.5}$) in adult subjects with COPD. In children not receiving antiinflammatory medication, same day indoor, outdoor, and central site exposures to $PM_{2.5}$ were associated with decrements in MMEF, PEF, and $FEV_1$. Associations with $PM_{2.5}$ and lung function decrements were also observed for 1-day lagged indoor (MMEF, PEF, $FEV_1$) and personal (PEF only) exposures. Antiinflammatory medication use in children significantly attenuated the PM effect on airflow rates and volumes.
*Conclusions:* This study found [redacted] in children with asthma who were not receiving medications. It is notable that [redacted] These findings suggest the need for future larger studies of PM effects in this susceptible population that repeatedly measure spirometry to include MMEF and potentially more sensitive markers of airway inflammation such as exhaled breath condensate and exhaled nitric oxide. *(CHEST 2006; 129:1614–1622)*

**Trenga, CHEST 2006**

# Air pollution and lung function among susceptible adult subjects: a panel study

Susanna Lagorio*[1], Francesco Forastiere[2], Riccardo Pistelli[3], Ivano Iavarone[4], Paola Michelozzi[2], Valeria Fano[2], Achille Marconi[4], Giovanni Ziemacki[4] and Bart D Ostro[5]

*Environmental Health: A Global Access Science Source* 2006, **5**:11

**Background**: Adverse health effects at relatively low levels of ambient air pollution have consistently been reported in the last years. We conducted a time-series panel study of subjects with chronic obstructive pulmonary disease (COPD), asthma, and ischemic heart disease (IHD) to evaluate whether daily levels of air pollutants have a measurable impact on the lung function of adult subjects with pre-existing lung or heart diseases.

**Methods**: Twenty-nine patients with COPD, asthma, or IHD underwent repeated lung function tests by supervised spirometry in two one-month surveys. Daily samples of coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$) particulate matter were collected by means of dichotomous samplers, and the dust was gravimetrically analyzed. The particulate content of selected metals (cadmium, chrome, iron, nickel, lead, platinum, vanadium, and zinc) was determined by atomic absorption spectrometry. Ambient concentrations of nitrogen dioxide ($NO_2$), carbon monoxide (CO), ozone ($O_3$), and sulphur dioxide ($SO_2$) were obtained from the regional air-quality monitoring network. The relationships between concentrations of air pollutants and lung function parameters were analyzed by generalized estimating equations (GEE) for panel data.

**Results**: Decrements in lung function indices (FVC and/or $FEV_1$) associated with increasing concentrations of $PM_{2.5}$, $NO_2$ and some metals (especially zinc and iron) were observed in COPD cases. Among the asthmatics, $NO_2$ was associated with a decrease in $FEV_1$. No association between average ambient concentrations of any air pollutant and lung function was observed among IHD cases.

**Conclusion**: This study suggests that the short-term negative impact of exposure to air pollutants on respiratory volume and flow is limited to individuals with already impaired respiratory function. The fine fraction of ambient PM seems responsible for the observed effects among COPD cases, with zinc and iron having a potential role via oxidative stress. The respiratory function of the relatively young and mild asthmatics included in this study seems to worsen when ambient levels of $NO_2$ increase.

**Lagorio, Envir Health 2006**

# Air Pollution and Incidence of Cardiac Arrhythmia

Peters, Annette1 2; Liu, Emerson3; Verrier, Richard L.3; Schwartz, Joel1; Gold, Diane R.1; Mittleman, Murray3; Baliff, Jeff1; Oh, J. Annie4; Allen, George4; Monahan, Kevin3; Dockery, Douglas W.1

Epidemiology 2000; 11:11-17

Air pollution episodes have been associated with increased cardiovascular hospital admissions and mortality in time-series studies.

We tested the hypothesis that patients with implanted cardioverter defibrillators experience potentially life-threatening arrhythmias after such air pollution episodes.

We compared defibrillator discharge interventions among 100 patients with such devices in eastern Massachusetts, according to variations in concentrations of particulate matter, black carbon, and gaseous air pollutants that were measured daily for the years 1995 through 1997.

A 26-ppb increase in nitrogen dioxide was associated with increased defibrillator interventions 2 days later (odds ratio = 1.8; 95% confidence interval = 1.1-2.9).

Patients with ten or more interventions experienced increased arrhythmias in association with nitrogen dioxide, carbon monoxide, black carbon, and fine particle mass. These results suggest that elevated levels air pollutants are associated with potentially life-threatening arrhythmia leading to therapeutic interventions by an implanted cardioverter defibrillator.

**Peters et al, Epidemiology 2000**

# Effects of particulate matter ($PM_{10}$, $PM_{2.5}$ and $PM_1$) on the cardiovascular system

Polichetti G, Cocco S, Spinali A, Trimarco V, Nunziata A

Toxicology 2009;261:1-8

Several studies have demonstrated that exposure to particulate matter (PM) of different size fractions is associated with an increased risk of cardiovascular disease (CVD). In this review, we have taken into consideration the possible correlation between the "short term" and "long term" effects of PM exposure and the onset of CVDs as well as the possible molecular mechanisms by which PM elicits the development of these events. Particularly, it is here underlined that these adverse health effects depend not only on the level of PM concentration in the air but also on its particular internal composition.

Furthermore, we have also synthesized the findings gleaned from those few studies indicating that PM produced by tobacco smoke can give rise to cardiovascular injury

Polichetti et Al, Toxicology 2009;261:1-8

Much remains to be discovered about particulate matter air pollution:

§ to determine the nature of the components of PM in all its size fractions

§ to investigate the incidence and effects of "*coarse particles" on CVD, alongside* the "*fine particles" and the "ultrafine particles"*

§ to understand more about the possible synergic action between toxicants present in cigarette smoke, PM in mainstream or sidestream cigarette smoke, and environmental PM

§ to further clarify the distinction between long and short-term effects of PM on CVD

§ more research is warranted to better examine the molecular mechanisms underlying the effects of PM on the cardiovascular system

Polichetti et Al, Toxicology 2009;261:1-8

# AIM

The aim of this pilot study is to evaluate the feasibility of performing epidemiological studies for assessing short-term effects of exposure to air pollutants in subjects with pre-existing lung or heart diseases in Italy

# METHODS

Study design: 2 panel studies will be conducted:

1.Palermo

2.Pisa

Population: To assess the short term respiratory and cardiovascular effects, all patients living in urban areas of Pisa and palermo will be eligible for the study

**1a.** 10 adult subjects with **COPD** diagnosis. The subjects will be selected among outpatients of the CNR Institute of Biomedicine and Molecular Immunology or of the University Hospital of Palermo. Eligible for the study will be subjects with $FEV_1$ between 30% and 70% of predicted, non current smokers

**1b.** 10 children with **asthma** diagnosis. The subjects will be selected among outpatients of the CNR Institute of Biomedicine and Molecular Immunology or of the University Hospital of Palermo. Eligible for the study will be subjects with mild-intermittent disease, non current smokers

**2.** 10 adult subjects with **arrhythmia**.

The subjects will be selected among outpatients of the CNR Institute of Clinical Physiology of Pisa.

Eligible for the study will be subjects with implanted cardioverter defibrillators, with no respiratory diseases, no current smokers

# Health outcomes

**Respiratory**

**Cardiovascular**

## Markers of disease

cardio-respiratory symptoms, mortality, hospital admissions

**$FEV_1$**
**FVC**
**$FEF_{25-75\%}$**
**PEF variability**
**Exhaled NO**

**Delivered electric shocks**

# Environmental outcomes 1

**To be evaluated under the responsibility of DM**

§ Daily concentration of

- $NO_2$
- CO
- $O_3$
- $PM_{10}$

will be recorded by fixed monitoring air-quality stations in Pisa and Palermo

# Environmental outcomes 2

**To be evaluated under the responsibility of DTA**

§ UFPs will be collected using a real-time condensation particle counter

§ Data on ultrafine particles size distribution will be used to calculate the particle number concentration (PNC) (1,000/$cm^3$)

# Protocol

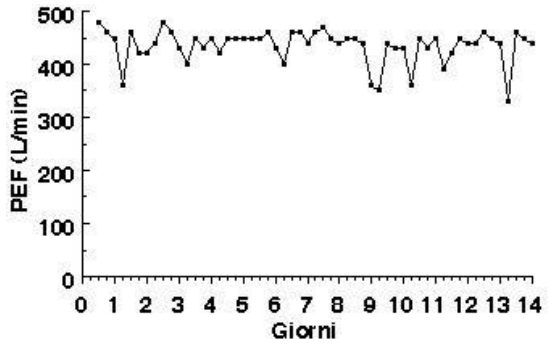
**Field working period**: the time period of interest will consist of 2 months in the summer period and 2 months in the winter period. The choice of the months will depend on historical time series analysis of air pollution levels in Pisa and Palermo

**Environmental data**: daily concentration of the air pollutants will be recorded during the field working period.

**Health data**:

**1.** Each subject affected by **respiratory diseases** will perform:

- two series of PEF measurements per day
- a daily diary to record acute symptoms and other outcomes
- spirometry
- exhaled NO (only in asthmatic children)
- visits will occur 4 times for season (every 15 days)




**2.** For each subject affected by **arrhythmia**:

- defibrillator discharge interventions will be available for the study time period
- each subject will fill a daily diary to record acute symptoms and other outcomes

§ A baseline questionnaire will be interviewer-administered at the enrollment:

- cardio-respiratory diseases/symptoms
- habitual use of drugs and risk factors:
- previous smoking habit
- exposure to occupational agents
- exposure to ETS…

§ A daily diary will be filled in by each subject to assess:

- activity pattern
- medical/emergency room visits
- school/working absenteeism
- use of short-term acting drugs
- acute respiratory-cardiovascular symptoms
- dietary intake
- PEF measurements during the two bimestrial periods

§ Data regarding possible hospital discharges or deaths of the investigated subjects will be collected during the two bimestrial periods comprising the intermediate months

# Expected Results

§ Evaluation of the association between daily variation of UFPs and other air pollutants and respiratory and cardiovascular effects

# Study Time Period

§ 12 months (4 months for organizational phase, 4 months for field working, 4 months for statistical analyses and final report)