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ACUTE CARDIOVASCULAR EFFECTS OF EXPOSURE TO AIRBORNE PARTICULATE MATTER: A STUDY OF POSSIBLE PATHOGENETIC MECHANISMS

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Settore disciplinare MED44

One thought to hide many

A thousand thoughts to hide one

I dedicate this work to My Parents

And to Prof. Marco Maroni

Who started the PM-CARE Study in 2004

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ABSTRACT

Introduction Increased levels of particulate matter air pollution (PM) have been associated with increased cardiovascular morbidity and mortality, especially in elderly adults and in people suffering from cardiovascular or lung diseases. The mechanisms behind these effects are still unknown, although some hypothesis have been postulated that include a modification of autonomic regulation of heart rhythm and the induction of arrhythmic events. Which fraction of PM is the most harmful is still controversial, and few studies investigated the role of personal exposure to different fractions, and in particular ultrafine particles.

Aim The aim of this thesis is to assess: i) the association between the exposure to PM and the modification of HRV (an index of autonomic regulation of heart rhythm) and QTec (an index of a pro-arrhythmic status), both in healthy subjects and in subjects suffering from chronic ischemic heart disease or chronic lung disease; ii) the potential role of inflammation and baseline health status in these associations; iii) the role of different PM fractions in these associations.

Materials and methods 27 healthy individuals (*"Healthy" group*), 34 individuals with chronic ischemic heart disease (*Heart group*), 18 with chronic asthma or COPD (*Lung group*) underwent a 24-hour exposure/clinical evaluation protocol during their habitual activities, both in the warm season (Summer) and in the cold season (Winter). Individual exposure to UFPs, fine and coarse particles number concentration, gravimetric $PM_{2.5}$ and PM_{10} was assessed for each subject, along with a 24-hour ambulatory ECG, for the assessment of heart rate variability and QT period.

Mixed effects models were used to evaluate the associations between exposure to particles and clinical parameters, during 24-hour, day- and night-time.

Results The mean(±SD) age of the study population was 64(±10) years and 65% were male. 24-hour exposure levels to UFPs, $PM_{2.5}$ and PM_{10} (median (25^{th}-75^{th})) were 19.643 (14.520-30.328) #/cm^3, 33,5 (23,33-50,01) μg/m^3 and 43,33 (31,66-62,85) μg/m^3 respectively. Higher exposure was observed during day-time, except for particles in the accumulation mode ($FP_{0,3-1}$). A -5,69% (95% C.I. -10,76 to -0,62) and -8,61% (-17,57 to 0,35) decrease in night-time SDNN (night-SDNN) in the total sample and in the *Heart group* respectively, was observed for an interquartile range (IQR) increase in $FP_{0,3-1}$ during the night period (night-$FP_{0,3-1}$). The same, even stronger, association was observed between day-$FP_{0,3-1}$ and night-SDNN, and was confirmed in all groups. In subjects with higher levels of hsCRP, an increase in all night-time vagal indices (PNN50>HF>rMSSD) was observed in the totality of subjects for an IQR increase in day-$FP_{2.5-10}$, and confirmed in healthy subjects only. In all subjects with lower levels of hsCRP, a +12,21% (95% C.I. 2,67 to 22,64) and +7,09 (0,12 to 14,55) increase in night-HF for an IQR increase in night-$FP_{0,3-1}$ and in night-$FP_{2,5-10}$ respectively was found, coupled to a decrease in the LF/HF ratio. These findings were confirmed in healthy subjects only. These associations were even stronger between day-FP and night-HRV in the total sample, and confirmed in the "*Healthy*" and the *Heart groups*.

Discussion and conclusion

The observed results suggest a major role of fine particles leading to acute and delayed alteration in autonomic control of heart rhythm in healthy subjects and subjects with chronic ischemic heart disease, probably not related to inflammatory status. On the other hand, coarse particles possibly need higher concentrations to exert their effects on autonomic control of heart rhythm, and these effects could be linked to inflammatory mechanisms in healthy subjects. Ultrafine particles appear to be less involved in the observed associations.

1 INTRODUCTION

In the last decades there has been an explosive growth in research relevant to the health effects of airborne particulate matter (PM). Increased levels of PM have been associated with increased cardiovascular morbidity and mortality[1-6]. The associations have been especially strong among people with pre-existing cardiovascular disorders and pre-existing lung disease [7, 8]. The mechanisms behind these effects are still unknown, although some hypothesis have been postulated that include a modification of autonomic regulation of heart rhythm[9, 10] and the induction of arrhythmic events[11, 12].

1.1 *PARTICULATE MATTER*

1.1.1 Particle characteristics

Particulate matter (PM) is a complex mixture with components having diverse sources, chemical and physical characteristics, those could vary the potential of particles to cause injury. Particles are still generally classified by their aerodynamic properties, because these determine transport and removal processes in the air and deposition sites and clearance pathways within the respiratory tract. The aerodynamic diameter is used as the summary indicator of particle size and corresponds to the size of a unit-density sphere with the same aerodynamic characteristics as the particle of interest.

Aerosol scientists use three different approaches or conventions in the classification of particles by size[13]:

1. Modes, based on the observed size distributions and formation mechanisms;
2. Dosimetry or occupational health size, based on the entrance into various compartments of the respiratory system;
3. Cut point, usually based on the 50% cut point of the specific sampling device, including legally specified, regulatory sizes for air quality standards.

1) The modal classification was proposed first by Whitby in 1978. The size distribution typically has three peaks (modes): coarse particles mode (5-30μm); accumulation mode (0,1-1μm); nuclei mode (15-100nm). An idealized size distribution showing modes and formation mechanisms is shown in Figure 1-I.B. The number, surface area and volume distributions for these modes of distribution are shown in Figure 1-I.A. Most particles are below 100 nm (ultrafine particles, UFPs), whereas most of the particles volume (and therefore most of the mass) is found in particles > 100 nm. 2) The occupational health community has defined size fractions in terms of their entrance into various compartments of the respiratory system, i.e.

inhalable particles (A_D<100μm), those particles enter into respiratory tract, including head airways, thoracic particles (A_D<10μm), those travel past the larynx and reach the lung airways and respirable particles (A_D<2.5μm), a subset of thoracic particles that are more likely to reach the gas-exchange region of the lung. 3) Another way to define particle size is to refer at size-selective sampling below or within a specific aerodynamic size range. PM_{10} includes those inhalable particles that are sufficiently small to penetrate into the thoracic region; the fine fraction of PM_{10} is cut off from the coarse fraction at 2.5 μm in aerodynamic diameter ($PM_{2.5}$), a size fraction with a high probability of deposition in the smaller conducting airways and alveoli.

In urban atmospheres, PM can generally be separated into three major fractions on the basis of particle size: coarse particles larger than 2.5 μm in aerodynamic diameter, fine particles smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and UFPs, smaller than 100 nm.

Sources. Particles in the coarse fraction or mode, are mostly mechanically produced by the break-up of larger solid particles. Human and natural sources may contribute to this mode, e.g. earth's crustal materials, dust, fly ash, pollen grains, bacterial fragments, sea spray etc.. Smaller particles (D_A < 2.5 μm) are largely formed from gases, but combustion processes may also generate primary particles in this size range. Typically, these particles originate as ultrafine particles produced by nucleation–condensation of low-vapour-pressure substances formed by high-temperature vaporization or by chemical reactions in the atmosphere to form very small particles (nuclei). Particles in this nucleation range or mode subsequently grow by coagulation or by condensation on the surface of existing particles. The efficiency of both coagulation and condensation decreases as particle size increases, and this decreasing efficiency effectively results in an upper limit of approximately 1 μm. Thus, particles tend to "accumulate" in a size range of 0.1–1μm, the so called "accumulation mode". So called secondary submicrometer-sized particles can also be produced by the condensation of metals or organic compounds that are vaporized in high-temperature combustion processes, and by the condensation of gases that have been converted in atmospheric reactions to low-vapour-pressure substances. The main precursor gases are sulfur dioxide, nitrogen oxides, ammonia and volatile organic compounds.

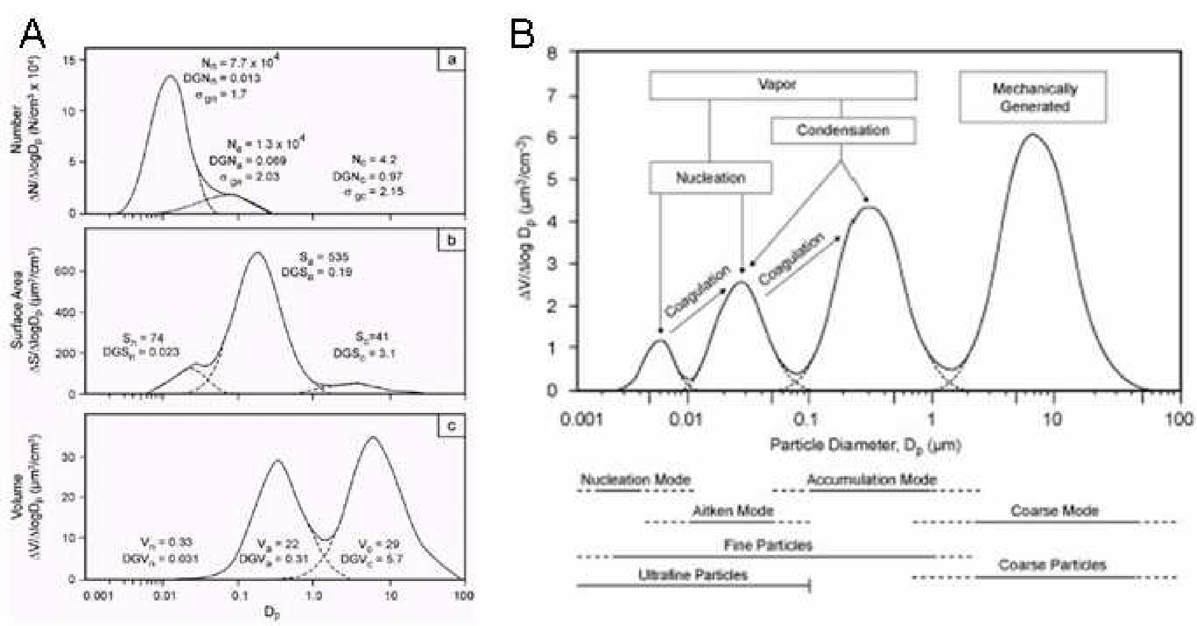

Figure 1-I.A Distribution of coarse (c), accumulation (a), and nuclei (n) mode particles by three characteristics, a)number (N), b) surface area (S) and c) volume (V) for the grand average continental size distribution. DGV= geometric mean diameter by volume; DGS= geometric mean diameter by surface area; DGN= geometric mean diameter by number; Dp=particle diameter. **Figure 1-I.B** An idealized size distribution, as might be observed in traffic, showing fine and coarse particles an the nucleation, Aitken, and accumulation modes that comprise fine particles. Also shown are the major formation and growth mechanisms of the four modes of atmospheric particles.[13]

Ultrafine particles are typically generated by combustion processes or formed from gaseous pollutants by photo-oxidation. Under typical urban conditions the half-life is around one hour for 20-nm particles[14]. Ultrafine particles are usually formed by nucleation. High concentrations of ultrafine particles are recorded immediately adjacent to busy roads, with concentrations decreasingly rapidly at increasing distance from roadways[15]. There is higher spatial variability for ultrafine particles than for fine particles in urban areas.

1.1.2 Particulate Matter Monitoring

In the general population, urban particulate matter exposure in its granulometric fractions have been up to now mainly acquired from fixed monitoring stations present in the urban areas [1, 16, 17]. European citizens spend on average over 90% of their time indoors. Indoor air particulate matter originates both from outdoors and from indoor sources, and the combination of the generally higher indoor concentrations and the overwhelming fraction of time spent indoors results in the overall domination of indoor air in air pollution exposures – and their respective health consequences - regardless of whether the sources are indoors or outdoors. Given that studies on personal/micro-environmental exposure to PM_{10} and $PM_{2.5}$ show a very modest correlation between personal exposure values and the levels of pollutants measured through the monitoring nets [18, 19], ambient levels do not necessarily estimate accurately individual exposure. However, personal exposure data, that represent an essential requirement for the health risk assessment, are still rather limited. Among the few available studies, between 1996 and 1997 the EXPOLIS study measured the personal exposures to key air pollutants, invluding particulate matter, in Milan and in other five European cities[20, 21].

1.2 *HEALTH EFFECTS OF PARTICULATE MATTER*

Particulate matter exposure has been associated with increased risk of cardiovascular mortality and morbidity–e.g. acute myocardial infarction, acute heart failure, angina exhacerbation, ischemic stroke, etc. [17, 22-26].

The mechanisms urban air particles cause these effects through are not known, although some hypothesis have been postulated, as summarized in Figure 1-II. There are three putative 'general' pathways: (1) autonomic mechanisms [e.g.PSNS (parasympathetic nervous system) withdraw and/or SNS (sympathetic nervous system) activation]; (2) the release of circulating pro-oxidative and/or pro-inflammatory mediators from the lungs (e.g. cytokines and activated immune cells) into the systemic circulation following PM inhalation that, in turn, indirectly mediate CV responses; and (3) ultrafine particles (UFPs) and/or soluble PM constituents translocating into the systemic circulation after inhalation that then directly interact with the CV system. The three general pathways are not mutually exclusive. They may overlap temporally and/or be principally activated at differing time points.

Pathway 1 may be partially, whereas pathway 3 may be entirely, initiated without requiring the generation of lung inflammation. PM deposited in the pulmonary tree can directly stimulate lung nerve reflexes via irritant receptors and, consequently, alter systemic autonomic balance.

Most end points pertaining to pathway 2 share a single common aetiology: pulmonary tissue oxidative stress induced by PM inhalation. Pro-oxidative PM constituents might thus directly interact with the vasculature and promote harmful CV responses. Inhaled ambient air particles could increase production of reactive oxygen species (ROS) in the airways and the lung alveoli[27, 28] and stimulate a local inflammatory reaction in the lungs[29-32]. The ROS and pro-inflammatory cytokines released into the blood stream[29] can affect blood pressure[33, 34], vascular tone and reactivity[35, 36], blood coagulability[37-39], progression of atherosclerosis[40-44] and also can affect autonomic cardiac control (heart rate, heart rate variability, and cardiac contractility)[45-47].

Soluble compounds and/or UFPs may rapidly translocate into the pulmonary circulation[48-50] and, subsequently, be transported throughout the systemic circulation, inducing oxidative stress and pro-inflammatory changes directly in the cardiac muscle and vasculature[51]. Lung- and circulation-mediated as well as direct patho-physiological mechanisms exacerbate myocardial ischemia and increase cardiovascular mortality.

The types and sizes of pollutants inhaled may determine their toxicity and the relative importance of the pathways. Larger fine or coarse PM cannot be transported into the circulation and will require secondary neural or pro-inflammatory responses to mediate extra-pulmonary actions, whereas ultrafine PM (or soluble constituents of larger particles) might directly enter the blood stream. A PM mixture rich in pro-oxidative combustion particles (e.g. organic carbon compounds and metals) might trigger more robust responses in a more rapid fashion which differs from less toxic inert PM.

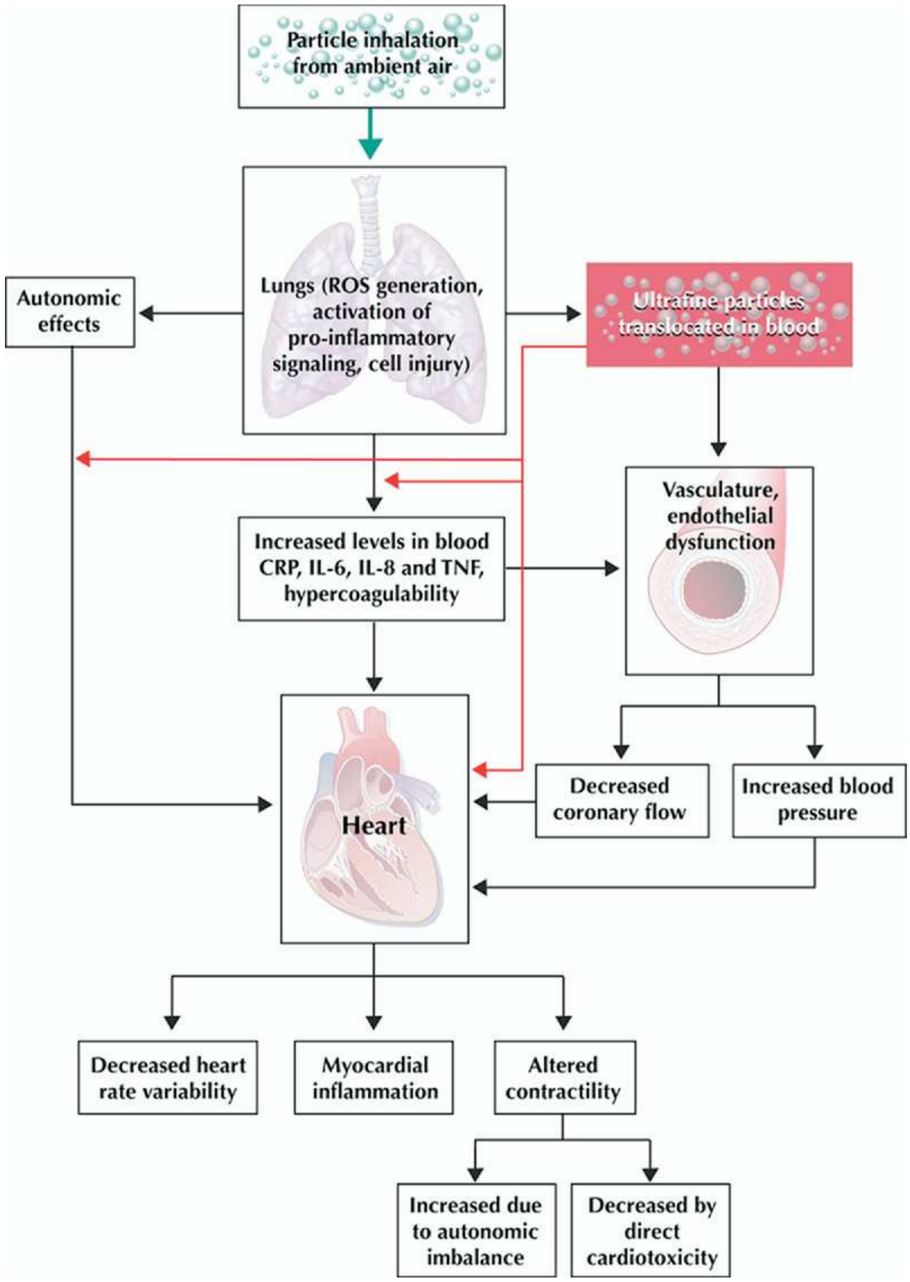

Figure 1-II Pathophysiological Mechanisms of Lung- and Circulation-Mediated Cardiovascular Toxicity of Particulate Air Pollutants. CRP C-reactive protein; IL interleukin; TNF tumor necrosis factor. Figure illustration by Rob Flewell from Simkovich (2008)[52].

1.3 FURTHER RESEARCH NEEDS

On this basis, there are needs for further investigation on the mechanisms behind the observed health effects of particulate matter, the identification of susceptible subjects, the role of different fractions of PM evaluated by personal exposure assessment, and the definition of the indoor and outdoor environment contributions to the total personal exposure.

HRV has been used frequently in air pollution research as a signal of cardiovascular effect, and to explore for potential patho-physiological mechanisms by which air pollution may lead to cardiovascular mortality and morbidity. The previously observed effects of air pollutants on HRV are not entirely consistent across studies (see Table 1-I), and some authors even did not find any relationship between PM exposure and HRV in elderly subjects[53, 54], in subjects with or without CVD[55], or at high exposure levels[56, 57]. Moreover, the role of inflammation in this hypothesised pathway is not well established.

Moreover, one major goal in air pollution research is the identification of those subjects in the general population who are more susceptible to develop adverse effects after the exposure. There are several categories of individuals within the general population that might be at higher risk for air pollution–mediated cardiovascular morbidity. These categories include people with pre-existing cardiovascular disease, people with chronic lung disease, and elderly individuals[58-60].

Up to now a few studies on human have investigated the role of ultrafine particles (UFPs) in altering autonomic control of heart rhythm and arrhythmia predisposition [54, 61], although among the different fractions of particulate matter UFPs could represent the most harmful fraction, due to the large surface area and the possibility of direct translocation from the respiratory tree to the blood stream[48-50].

This thesis is a part of a more comprehensive study started by professor Marco Maroni in 2004, the PM-CARE Study, *Particulate Matter Cardio-Respiratory Effects*, that aimed to further investigate this open research areas.

Table 1-I Studies about heart rate variability and particulate matter association in humans.

Reference	Population	HRV Indices	PM	Association with PM increase
Liao et al, 1999[62]	**26 elderly**	SDNN, LF, HF	$PM_{2.5}$	↓ HRV
Pope et al, 1999[45]	**6 elderly and 1 adult with CVD**	HR, SDNN, SDANN, rMSSD	PM_{10}	↑ HR, rMSSD ↓ SDNN, SDANN
Gold et al, 2000[46]	**21 elderly**	SDNN, rMSSD	$PM_{2.5}$ PM_{10}	↓ HRV with $PM_{2.5}$
Brauer et al, 2001[53]	**16 elderly**	HR, SDNN	$PM_{2.5}$ PM_{10}	No association
Creason et al, 2001[63]	**56 elderly**	HF	$PM_{2.5}$, PM_{10}	↓ HF wit $PM_{2.5}$
Magari et al, 2001[64]	40 boilermakers	SDNN	$PM_{2.5}$[a]	↓ SDNN
Magari et al, 2002[65]	39 boilermakers	SDNN	$PM_{2.5}$	↑ SDNN higher for vanadium and lead
Magari et al, 2002[66]	20 boilermakers	SDNN	$PM_{2.5}$	↓ SDNN
Devlin et al, 2003[59]	**10 healthy elderly**	SDNN, PNN50, LF, HF	CAPs[b]	↓ SDNN, PNN50, HF after exposure
Holguin et al, 2003[67]	**34 elderly**	LF, HF, LF/HF	$PM_{2.5}$	↓ HF when adj for O_3
Chan et al, 2004[61]	**9 young, 10 adults with lung function impairment**	SDNN, rMSSD, LF, HF	UFPs[a]	↓ HRV
Liao et al, 2004[68]	6784 middle aged	SDNN, LF, HF	PM_{10}	↓ SDNN, HF
Pope et al, 2004[60]	88 middle aged	SDNN, SDANN, rMSSD	$PM_{2.5}$	↓ SDNN, rMSSD
Riediker et al, 2004[69]	10 healthy young	SDNN, PNN50, LF, HF, LF/HF	$PM_{2.5}$	↑ SDNN, PNN50, HF ↓ LF/HF
Chuang et al, 2005[70]	**26 adults with CVD**	SDNN, rMSSD, LF, HF, LF/HF	$PM_{0,3-1}$[a], $PM_{1-2,5}$[a], $PM_{2,5-10}$[a],	↓ SDNN, rMSSD with $PM_{0,3-1}$ ↓ LF, HF with $PM_{0,3-1}$ in hypertensive subjects
Ebelt et al, 2005[71]	**16 elderly with COPD**	SDNN, rMSSD	$PM_{2.5}$[c], PM_{10}	↓ rMSSD with PM_{10}
Park et al, 2005[72]	**497 elderly male with CVD**	SDNN, rMSSD, LF, HF, LF/HF	$PM_{2.5}$, BC	↓ HF and ↑ LF/HF with $PM_{2.5}$ ↓ LF, LF/HF with BC
Schwartz et al, 2005[73]	**28 elderly**	SDNN, rMSSD, PNN50, LF/HF	$PM_{2.5}$, BC	↓ rMSSD, PNN50 with $PM_{2.5}$ ↓SDNN, LF/HF with BC
Schwartz et al, 2005[74]	**497 elderly males with CVD**	HF	$PM_{2.5}$	↓ HF in subjects without allele GSTM1 (impaired defese against ROS).
Sullivan et al, 2005[55]	**34 elderly with (21) and without (13) CVD**	SDNN, SDANN, rMSSD, LF, HF, VLF	$PM_{2.5}$	No association
Luttmann-Gibson et al, 2006[75]	**32 elderly**	SDNN, rMSSD, PNN50, LF, HF	$PM_{2.5}$	↓ HRV

Reference	Population	HRV Indices	PM	Association with PM increase
Lipsett et al, 2006[76]	**19 nonsmoking adults with CAD**	SDNN, SDANN	$PM_{2.5}$, $PM_{2.5-10}$, PM_{10}	↓ SDNN, SDANN with $PM_{2.5-10}$ and PM_{10} No association with $PM_{2.5}$
Timonen et al, 2006[77]	**132 elderly** (in three cities)	SDNN, rMSSD, LF, HF, LF/HF	UFPs, $FP_{0,1-1}$, $PM_{2.5}$	↓ LF/HF with UFPs Controversial findings for LF, LF/HF with $PM_{2.5}$ in different cities
Wheeler et al, 2006[47]	**18 adults with COPD, 12 adults with MI**	SDNN	$PM_{2.5}$	↑ SDNN in COPD ↓ SDNN in MI (not significant).
Adar et al, 2007[78]	**44 elderly**	HR, SDNN, rMSSD, PNN50, LF, HF, LF/HF	$PM_{2.5}$, $FP_{0,3-,.5}$, $CP_{2,5-10}$	↓ in all HRV indices excepted ↑ in HR, LF/HF for $PM_{2.5}$, $FP_{0,3-,.5}$
Cavallari et al, 2007[79]	36 boilermakers	Night-time SDNN, rMSSD	$PM_{2.5}$	↓ Night-time HRV
Chahine et al,2007[80]	**539 elderly males with CVD**	SDNN, HF, LF	$PM_{2.5}$	↓ HRV in subjects with impaired defence against ROS
Chen et al, 2007[81]	18 boilermakers obese and non	HR, SDNN, rMSSD	$PM_{2.5}$	↓ HRV 2-4 fold greater in obese
Chuang et al, 2007[82]	**46 adults with or at risk for CVD**	SDNN, rMSSD, LF, HF	$PM_{2.5}$, PM_{10}	↓ HRV
Yeatts et al, 2007[83]	**20 asthmatic adults**	SDNN, ASDNN, SDANN, rMSSD, PNN50, LF, HF	$PM_{2.5}$ $PM_{2.5-10}$	↓ SDNN, ASDNN with $PM_{2.5-10}$, no association with $PM_{2.5}$
Scharrer et al, 2007[56]	20 healthy adults	SDNN, rMSSD, TP, LF, HF	Welding fumes[b]	No association
Baccarelli et al, 2008[84]	**549 elderly males with CVD**	SDNN	$PM_{2.5}$	↓ HRV in subjects with impaired methionine cycle
Barclay et al, 2008[54]	**132 non smoking elderly**	SDNN, SDANN, rMSSD, PNN50, LF, HF, LF/HF	UFPs, $PM_{2.5}$, PM_{10}	No association
Cavallari et al, 2008 [85]	36 boilermakers	SDNN	$PM_{2.5}$	↓ SDNN
Cavallari et al, 2008 (Environ Health) [86]	36 boilermakers	Night-time rMSSD	$PM_{2.5}$ metals	↓ night-time rMSSD, higher association with manganese, that did not explain all association
Peretz et al, 2008[57]	16 healthy young adults	SDNN, rMSSD, LF, HF; LF/HF	DE[b]	No association
Cardenas et al, 2008[87]	52 healthy adults	LF, HF, LF/HF	$PM_{2.5}$[a]	↓ LF, HF higher in subjects with positive tilt-test
Min et al, 2008[88]	**1349 elderly**	SDNN, LF	PM_{10}	↓SDNN, LF

Notes: [a] Personal monitoring; [b] Experimental exposure, [c] Both personal and ambient monitoring. SDNN, the standard deviation of all normal-to-normal (NN) intervals; rMSSD, the square root of the mean of the sum of the squares of differences between adjacent normal-to-normal (NN) intervals; PNN50, the proportion of adjacent normal-to-normal (NN) intervals differing by more than 50 ms; SDANN, the standard deviation of the average NN intervals in all 5-minute segments of the 24-hour period; LF, low frequency; HF, high frequency; PM_{10}, particulate matter <10 μm in aerodynamic diameter; $PM_{2.5}$, PM<2.5 μm in aerodynamic diameter; $PM_{0.3–1.0}$, particle sizes with aerodynamic diameters between 0.3 and 1.0 μm; $PM_{1–2.5}$, particle sizes with aerodynamic diameters between 1.0 and 2.5 _m; $PM_{2.5–10}$, particle sizes with aerodynamic diameters between 2.5 and 10 μm m; UFPs, number concentrations of submicrometer particles with a size range of 0.02–1.0 μm; BC, black carbon; elemental carbon; DE, diesel exhaust.

2 AIM

The aims of this thesis are to assess, in healthy subjects and in subjects suffering from chronic ischemic heart disease or chronic lung disease:

1) the association between the exposure to particulate matter and the modification of autonomic regulation of heart rhythm;
2) the association between the exposure to particulate matter and the induction of a pro-arrhythmic status;
3) the potential role of inflammation in these associations;
4) the potential differences in susceptibility due to baseline health conditions;
5) the role of each fraction of particulate in these associations.

3 Materials And Methods

Data were collected as part of the PM-CARE Study, *Particulate Matter Cardio-Respiratory Effects*, a more comprehensive investigation designed to examine mechanisms behind observed cardio-respiratory effects of exposure to air particulate matter. Exposure and health measurements were made under a protocol approved by the Ethic Committee of the "Luigi Sacco" University Hospital (Milan, Italy) and the "San Gerardo" University Hospital (Monza, Italy), for individuals living in the urban and suburban area of Milan, Italy, between July 2005 and July 2006. Written informed consent was obtained.

Three groups of subjects were studied: subjects suffering from chronic ischemic heart disease, subjects suffering from asthma or chronic obstructive pulmonary disease (COPD) and subjects without diagnosis of the afore mentioned diseases. Each participant underwent a twenty-four hours protocol, during normal unrestricted out-of-hospital activity that included evaluation of exposure and health parameters twice, in the warm season (May – October) and in the cold season (November – April).

The monitoring protocol was started by trained physicians and technicians in the morning at each participants' home, and ended the following day at the hospital.

3.1 Study Subjects

Studied subjects were recruited from the patients community of two Italian hospitals ("Luigi Sacco" University Hospital and "San Gerardo" University Hospital), and grouped according to their health status into subjects suffering from chronic ischemic heart disease (*Heart Group*), subjects suffering from asthma or chronic obstructive pulmonary disease (COPD) (*Lung Group*) and subjects without diagnosis of the afore mentioned diseases (*"Healthy" Group*). During an initial ambulatory medical visit a questionnaire was administered regarding the subject's demographics, physiological and medical history, current medication use, educational qualification and job position, usual sport activities intensity, alcohol consumption, smoking history and second-hand smoke (SHS) exposure at home. A 12-lead ECG and lung function tests were performed. A blood sample was collected for blood test analysis.

General exclusion criteria included current smokers (or ex-smokers < 6 months), poor glycemic control (sHbA1c > 7%, as defined by the "American Diabetes Association" Guidelines[89], severe renal failure (serum creatinine > 2,5 mg/dL), moderate-to-severe anemia (Hb < 10 mg/dL), coagulation disorders (PLT < 150.000 mg/dL; PT-INR < 0,8 or > 1,2; PTT < 21 or 36''; FG < 200 or > 400 mg/dL), electrolytic imbalance (Na+ < 135 or > 145 mEq/L; K+ < 3,4 or > 4,8 mEq/L).

Subjects in the *Heart Group* were eligible if they had chronic ischemic heart disease defined as 1) diagnosis of coronary artery disease (CAD) by at least one of the following: a) a positive coronarography, b) a positive provocative test (male), c) a positive myocardial scintigraphy (female); 2) a history of chronic stable angina; 3) a prior percutaneous coronary intervention (PTCA) or a prior coronary artery bypass surgery at least 6 months before recruitment; or 4) previous myocardial infarction at least 6 months before recruitment. Specific exclusion criteria for this group included unstable angina, angina in CANADIAN class 3a or 4a, acute cardiovascular events in the previous 6 months, heart failure in NYHA class III and IV, anticoagulation therapy, paced rhythm (both pacemaker and implantable cardioverter defibrillator > 5% of R), chronic atrial fibrillation, moderate-to-severe COPD or asthma. Subjects in the *Lung group* were eligible if they had 1) mild-to-severe COPD (as defined by GOLD guidelines [90, 91]; 2) mild-to-severe asthma (as defined by GINA guidelines[92]. Specific exclusion criteria for this group included a vital capacity less than 2 liters and chronic ischemic heart disease. Subjects in the *"Healthy" Group* were eligible if they had 1) normal ECG and no heart disease; 2) normal lung function tests and no lung disease. Specific exclusion criteria for this group included upper airways disease (included nasal and paranasal sinus disease), renal disease, allergy, and diabetes mellitus.

112 individuals were screened, 16 did not match the selection criteria and 5 did not accept to undergo the protocol for compliance reasons. 81 subjects have been studied: 27 in the *"Healthy" Group*, 34 in the *Heart Group* and 20 in the *Lung Group*.

3.2 INDIVIDUAL EXPOSURE AND MICROCLIMATIC MONITORING

Exposure measurements were performed using individual monitoring instruments. All devices were assembled on a mobile monitoring unit (MMU), that was equipped to provide self-contained and unattended 24-hour monitoring, and that was easily transportable by the participants during their displacements (Figure 3-I).

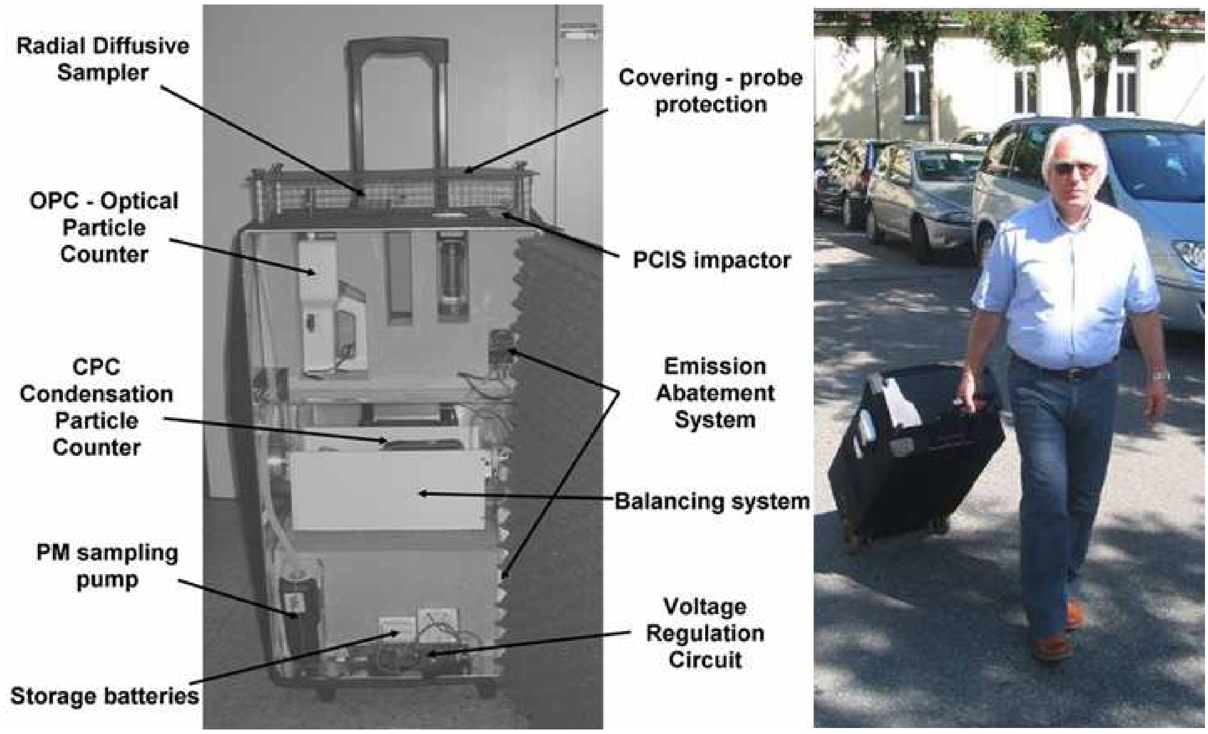

Figure 3-I The Mobile Monitoring Unit(MMU).

The protocol included measurements of ultrafine particles number concentration (UFPs), fine particles and coarse particles number concentration, PM_1, $PM_{2.5}$, PM_{10} mass fractions and microclimatic parameters (temperature and relative humidity).

3.2.1 Ultrafine particles

UFPs number concentration was continuously measured with a Condensation Particle Counter (CPC, P-TRAK® Ultrafine Particle Counter, TSI Model 8525) for particles in the size range 0.02–1 µm in aerodynamic diameter (D_A) (acquisition time:30 s). Data were recorded by an internal data-logger and downloaded on computer at the end of each 24-hour monitoring period with TrakPro software (Version 3.6.2.0, TSI Inc.).

3.2.2 Number concentration of particles having aerodynamic diameter larger than 0,3μm

An Optical Particle Counter (OPC, Lighthouse Handheld 3016 Particle Counter) was used to measure the number of particles having D_A>0,3μm, sorted into six dimensional classes (0.3-0.5; 0.5-1.0; 1.0-2.5; 2.5-5.0; 5.0-10; >10μm). Three measures were included in statistical models: fine particles (FP) in the accumulation mode, as the sum of 0.3-0.5 and 0.5-1.0μm fractions ($FP_{0.3-1}$), larger fine particles as 1.0-2.5μm fraction ($FP_{1-2.5}$), and coarse particles (CP), as the sum of 2.5-5.0; 5.0-10μm fractions.

3.2.3 PM mass fractions.

Twenty four hours time weighted gravimetric measurements of PM were performed with a personal cascade impactor sampler (PCIS), with three impaction stages and an after-filter that allows the separation and collection of airborne particles in the following aerodynamic particle diameter ranges: <0.5, 0.5–1.0, 1.0–2.5 and 2.5–10 μm. The PCIS operates in combination with the Leland Legacy Sample Pump (SKC Inc., Cat. No. 100–3000) at a flow rate of 9 L/min. PTFE membranes with PTFE support were used for collection of PM fractions. Membrane filters were weighted according to UNI EN 12341. Four gravimetric measures were included in statistical models: PM_1, as the sum of fractions less than 1 μm in aerodynamic diameter, $PM_{2.5}$, as the sum of fractions less than 2.5 μm, $PM_{2.5-10}$ fraction and PM_{10}, as the sum of fractions less than 10 μm.

3.2.4 Microclimatic Parameters.

Temperature and Relative Humidity (RH%) were continuously measured with a miniaturized microclimatic probe (Lighthouse Worldwide Sol.). Data were logged with an acquisition time of 30s and downloaded on a computer at the end of each 24-hour monitoring period.

3.3 *HEALTH MONITORING*

24-hour ambulatory ECGs were obtained in all subjects during normal unrestricted out-of-hospital activity. ECGs were recorded digitally with a sampling rate of 200 Hz (5 msec) on removable secure digital card (SD 64MB) using a lightweight, 7 leads (three-channel XYZ) ECG Holter monitor (SpiderViewTM; Ela Medical; C.A. La Boursidière – 92357 Le Plessis-Robinson Cedex – France). 24-hour ambulatory ECGs were then analysed using Synescope™ Holter analysis software for multichannel multiday recordings Version 1.0 (Ela Medical; C.A. La Boursidière – 92357 Le Plessis-Robinson Cedex – France). The QRS complexes were automatically classified and manually verified by a blinded trained physician as normal sinus rhythm, atrial or ventricular premature beats, or artifacts. Ectopic beats, arrhythmic periods and artifacts were linearly interpolated. ECGs with more than 5% ectopic beats and/or artifacts were excluded from analysis.

3.3.1 HRV Analysis.

HRV is a measure of the balance between sympathetic mediators of heart rate (HR) (i.e. the effect of epinephrine and norepinephrine, released from sympathetic nerve fibres, acting on the sino-atrial and atrio-ventricular nodes), which increase the rate of cardiac contraction and facilitate conduction at the atrio-ventricular node, and parasympathetic mediators of HR (i.e. the influence of acetylcholine, released by the parasympathetic nerve fibres, acting on the sino-atrial and atrio-ventricular nodes), leading to a decrease in the HR and a slowing of conduction at the atrio-ventricular node[93]. The last three decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality[94-97]. Experimental evidence suggested an association between propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity and heart rate variability (HRV) represents one of the most promising quantitative markers of autonomic activity[93]. The variations in heart rate may be evaluated by a number of methods, that included the time domain measures and the frequency domain. Both methods are based on the determination of intervals between successive normal complexes: in a continuous ECG record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) are determined.

In this study, 24-hour ambulatory ECGs were analyzed in the time and frequency domains over the entire 24-hour recording, day-time and night-time. The statistical time domain measures investigated included:

- SDNN [ms], the standard deviation of the NN intervals, that is, the square root of variance;
- SDANN [ms], the standard deviation of the average NN intervals calculated over short periods, usually 5';
- rMSSD [ms], the square root of the mean squared differences of successive NN intervals;
- pNN50 [%], the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms (NN50) by the total number of NN intervals.

Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency, by using proper mathematical algorithms. In this study, the nonparametric fast Fourier transform (FFT) method was used for analysis in the frequency domain from long-term recordings (i.e. 24-hours, day and night), allowing the identification of three main spectral components: very low frequency (VLF), low frequency (LF) and high frequency (HF). The measurement of total power (TP), VLF, LF, and HF was made in absolute values of power (ms^2), and LF and HF were also measured in normalized units, which represent the relative value of each power component in proportion to the TP minus the VLF component[98, 99]. Also the LF/HF ratio was assessed. Frequency ranges were as follows: very low frequency (VLF) <0.04 Hz, LF between 0.04 to 0.15 Hz, HF between 0.15 to 0.4 Hz.

3.3.2 QT interval measurement

The QT period or interval corresponds to the period between Q wave, i.e. ventricular depolarization, and the end of the T wave, i.e. ventricular repolarization, in the ECG. Long QT period, both congenital or drug induced, has been linked to arrhythmias and sudden death.

QT intervals were automatically measured on the 24-hour ambulatory ECGs obtained for the HRV analysis using a Synescope™ Holter analysis software, and accepted only after careful visual inspection by a blinded trained physician. QT was measured from the onset of the Q wave to the end of the T wave (QTe). The software provided automatically the corrected QTe interval using the formula: $QTec = QTe/(RR)^{1/2}$ (RR = interval between ventricular depolarizations).

3.3.3 High-sensitivity C-reactive protein (hsCRP)

Fasting blood sample was obtained from the antecubital vein at the end of each 24-hour monitoring protocol at the hospital. High-sensitivity C-reactive protein serum concentration was immediately measured at the "Luigi Sacco" University Hospital clinical laboratory by a two-site chemiluminescent enzyme immunometric assay (IMMULITE hs-CRP; Diagnostic Products Corp., CA).

3.4 *Statistic Analysis*

All data were tested for normality with Kolmogorov-Smirnov Test. For statistical analysis HRV indices and PM data were ln-transformed to achieve normality, where necessary. A p value < 0.05 was considered statistically significant.

To test differences in exposure levels and in clinical parameters among groups and between the warm and the cold season, the one way ANOVA test and the paired Student's T test were used respectively.

Data were collected continuously during 24-hours. Analysis were conducted on 24-hours, day (7 a.m. – 11 p.m.) and night (11 p.m. – 7 a.m.) means.

To estimate the relationship between pollutant and changes in health parameters (HRV indices and QTec) single pollutant mixed effects models were fitted for repeated measures and with random intercept for individuals, to account for the lack of independence due to repeated measures for each participant. Final models were corrected for age, gender, BMI, group, β-blockers, anti-hypertensive drugs (angiotensin-converting enzyme inhibitors, calcium channel blockers and diuretics drugs), alcohol consumption, high sensitivity C reactive protein and meteorological variables (temperature and relative humidity).

The analysis protocol included:

1) estimation of the associations existing between 24-hour exposure levels and health parameters in the 24-hours and during the day and night periods;
2) study of the relationship existing between daily exposure to particles and night-time health parameters, to eventually identify a delayed effect.

The analyses were conducted first in the total sample. If significant association were found, an interaction term PM*group was included in the mixed model, to assess differences in effects due to health conditions.

The same analysis protocol was adopted for HRV indices on subjects stratified by high or low levels of hsCRP levels, to assess differences due to the inflammatory status. The median value of observed hsCRP concentrations was chosen as cut-off (1,95 mg/L), in order to have two groups of homogeneous size.

For presentation purposes, all effect estimates (β) were transformed into percent changes per inter-quartile range (IQR) of a pollutant using the formula $(e^{(\beta * IQR)} - 1) * 100$ for ln-transformed data and $(\beta * IQR \div M) * 100$ for all the other outcomes, where M is the mean of the clinical parameter. Estimates are presented with their 95% confidence intervals.

4 RESULTS

4.1 *CHARACTERISTICS OF STUDIED SUBJECTS*

Measurements were performed in 81 individuals suffering from chronic ischemic heart disease (*Heart Group*; n=34) or from chronic lung disease (chronic obstructive pulmonary disease or asthma; *Lung Group*; n=20) and in individuals without diagnosis of the afore mentioned diseases (*"Healthy" Group*; n=27) over two 24-hour sessions.

Given that ectopic beats, arrhythmic events and artefacts may alter the estimation of the HRV and QTec, a cut-off of 5% of ectopic beats, arrhythmic events and/or artefacts was chosen to select ECGs suitable for HRV analysis. After editing, 131, 142 and 152 ambulatory ECGs were available for 24-hour, day-time and night-time HRV analysis respectively (< 5% ectopic beats, arrhythmic events and/or artefacts); wherease 128, 139 and 148 ECGs were available for QT period assessment during 24-hour, day-time and night-time respectively (< 5% ectopic beats, arrhythmic events and/or artefacts, and QT period assessed by the software). Analyses were conducted on 79 individuals with at least one ECG available for HRV and QT analysis (24-hour and/or daily and/or night-time) in the warm and/or in the cold season: 27 "healthy" individuals, 18 with chronic ischemic heart disease, and 34 with chronic lung disease.

Table 4-I shows the characteristics of the 79 subjects with available HRV and QT measurements and those of the subjects in the three groups. The mean age in the overall studied population was 64±10 years at the beginning of the study, and 65% were males; in the *"Healthy"*, the *Heart* and the *Lung Groups* mean age were 61±7 years, 66±10 years and 66±12 years, and male gender was 52%, 82% and 50% respectively. Subjects were generally overweight in all groups. No studied individual was a current smoker, although about half of them were former smokers. Less then 25% of individuals in the *Heart* and *Lung Group* suffered from diabetes mellitus, and 26%, 68%, 50% and of individuals suffered from hypertension in the "*Healthy*", in the *Heart* and in the *Lung Group* respectively. In the *Heart Group* the majority of subjects underwent a PTCA or coronary artery bypass surgery (79%), or had a history of myocardial infarction (68%). In the *Lung Group* 56% suffered from chronic obstructive pulmonary disease (COPD), 56% from asthma. Medications use differed in the three groups, depending on health status.

Table 4-I Characteristics of studied individuals (total sample and three groups). Demographic characteristics, physiological and medical history, drug assumption. [Data shown as mean±SD (min-max) or as n (%)].

	Total Group	"Healthy" Group	Heart Group	Lung Group
	n (%)	n (%)	n (%)	n (%)
Subjects [n]	79	27	34	18
Age [mean±SD (min-max)]	64 ± 10 (37 – 87)	61 ± 7 (52 - 78)	66±10 (45 - 87)	66 ± 12 (37 - 79)
BMI [mean±SD (min-max)]	27 ± 5 (18 - 45)	27 ± 4 (21 - 42)	26±4 (18 - 38)	29 ± 6 (20 - 45)
Gender	51 (65%)	14 (52%)	28 (82%)	9 (50%)
Alcohol assumption[a]	38 (48%)	15 (56%)	16 (47%)	7 (39%)

	Total Group	"Healthy" Group	Heart Group	Lung Group
	n (%)	n (%)	n (%)	n (%)
Physical activity[b]	33 (42%)	22 (81%)	7 (21%)	5 (28%)
Former smoker	43 (54%)	13 (48%)	22 (65%)	9 (50%)
Hypertension	39 (49%)	7 (26%)	23 (68%)	9 (50%)
Dyslipidemia	37 (47%)	13 (48%)	18 (53%)	6 (33%)
Diabetes Mellitus	10 (13%)	0 (0%)	7 (21%)	3 (17%)
hsCRP mg/L [median (25^{th}-75^{th})]	1,95 (0,7-4,1)	1,7 (0,5-3,8)	1,55(0,6-3,6)	2,2 (1,4-4,6)
Antihypertensive treatment[c]	38 (48%)	5 (19%)	26 (76%)	8 (44%)
β-blockers	28 (35%)	1 (4%)	26 (76%)	1 (6%)
Statin	28 (35%)	1 (4%)	26 (76%)	2 (11%)
Long acting β_2 agonist	10 (13%)	0 (0%)	0 (0%)	10 (56%)
CAD	13 (16%)	-	13 (38%)	-
Chronic Stable Angina	3 (4%)	-	3 (9%)	-
PTCA and/or by pass	27 (34%)	-	27 (79%)	-
Myocardial infarction	23 (29%)	-	23 (68%)	-
BPCO	10 (13%)	-	-	10 (56%)
Asthma	10 (13%)	-	-	10 (56%)

Notes: [a] Alcohol assumption more than two glasses per day; [b] Physical activity from moderate to intense; [c]Antihypertensive drugs: Calcium channels antagonist and/or ACE-inhibitors and/or Diuretics drugs.

4.2 Individual Exposure

Exposure data for almost all pollutants were available for at least one monitored period, i.e. summer and/or winter monitoring, for each studied subject. Results are presented as median (25^{th} -75^{th}). Individual exposure levels to all parameters did not differ in the three groups (test: one way ANOVA, $p<0,05$).

4.2.1 Individual exposure parameters measured during the 24-hour period.

130 measurements were available for the 24-hour period. Descriptive statistics for each investigated pollutant and meteorological values in the total sample are summarized in Table 4-II.a. In the total sample, the exposure levels (mean±SD) to $PM_{2.5}$ and PM_{10} were 41,53±22,52 μg/m³ and 51,97±24,31 μg/m³ respectively. Number concentration of UFPs (D_A > 20 nm) was 19643 (14520 - 30328) #/cm³.

Winter exposure levels were significantly higher for almost all the investigated PM fractions (paired Student's T test on available paired data, 56 subjects, $p<0,05$) (Table 4-II.b), with a mean Winter/Summer ratio of 2, 1.8 and 1.7 for PM1, $PM_{2.5}$ and PM_{10} respectively. The same trend was observed for UFPs, fine particles in the accumulation mode ($FP_{0.3-1}$), fine particles from 1 to 2.5 μm in D_A ($FP_{1-2.5}$), and coarse particles ($CP_{2.5-10}$), measured as particles number concentration (#/cm³).

Table 4-II.a Exposure during the 24-hour period, in Summer and Winter. Descriptive statistics of 24-hour exposure and meteorological parameters in the total sample. **Table 4-II.b** Differences between the two investigated period: warm period (Summer) and cold period (Winter). [Data shown as median (25th -75th)].

Table 4-II.a | **Table 4-II.b**

Particles	Summer + Winter	Summer	Winter	Student's T test[a]
	Median (25th -75th)	Median (25th -75th)	Median (25th -75th)	
Subjects [n]	75	67	63	
Measurements [n]	130	67	63	
UFPs 24h avg [#/cm³]	19643 (14520 - 30328)	16836 (12580 - 23977)	24710 (17560 - 32891)	*
PM_1 24h TWA [μg/m³]	27,67 (19,93-45,79)	22,48 (17,46 - 29,41)	42,5 (26,96 - 55,09)	*
$PM_{2,5}$ 24h TWA [μg/m³] (Mean±SD)	33,5 (23,33-50,01) 41,53±22,52	26,44 (21,12 - 35,25) 30,89±14,71	47,43 (31,91 - 60,17) 52,04±23,99	*
$PM_{2,5-10}$ 24h TWA [μg/m³]	8,95 (7,19-12,7)	10,11 (7,49 - 13,33)	8,22 (6,62 - 12,54)	
PM10 24h TWA [μg/m3] (Mean±SD)	43,33 (31,66-62,85) 51,97±24,31	35,27 (28,63 - 49,02) 41,92±18,32	56,98 (40,67 - 74,65) 61,89±25,50	*
FP_{03-1} 24h avg [#/cm³]	1023,7 (592,7-1879,7)	780,8 (430,8-1055,3)	1821,4 (1072,4-2640,9)	*

FP$_{1-2.5}$ 24h avg [#/cm^3]	5,2 (3,1-8,5)	3,8 (2,4-5,4)	7,5 (5,2-10,3)	*
CP$_{2,5-10}$ 24h avg [#/cm^3]	2,5 (1,6-3,9)	2,1 (1,5-3,4)	2,9 (2-4,8)	*
T 24h avg [°C]	25,39 (23,08-28,51)	28,47 (26,92 - 30,16)	23,18 (22,46 - 24,22)	
RH 24h avg [%]	37,76 (33,75-43,18)	42,7 (37,87 - 45,22)	34,44 (31,75 - 37,34)	

Notes: [a] Student's T test on paired data (56 subjects) (*p < 0,05).

4.2.2 Individual exposure parameters measured during day- and night-time

142 and 152 measurement were available for day period and night period respectively, for almost all parameters. Gravimetric measurements of PM were not available for day-time and night-time exposure assessment. Due to technical reasons, only 37 measurements of UFPs night-time levels were available.

Daily exposure levels were higher than night-time levels (Student's T test on paired data; $p<0,05$) for UFPs, FP$_{1-2.5}$ and coarse particles (see Table 4-III), with a mean day/night ratio of 1.9 and 2.9 for FP$_{1-2.5}$ and CP$_{2.5-10}$ respectively. Exposure levels to fine particles in the accumulation mode (FP$_{0.3-1}$) were comparable between day and night.

Table 4-III Differences between daily and night-time exposure levels in the total sample for UFPs, fine particles (FP$_{0.3-1}$ and FP$_{1-2.5}$) and coarse particles (CP$_{2.5-10}$).

Particles	Day Summer+Winter	Night Summer+Winter	Student's T test[b]
	Median (25th -75th)	Median (25th -75th)	
Subjects [n]	77	79	
Measurements [n]	142	152	
UFPs [#/cm^3][a]	18646 (14014-29410)	9752 (7214-13427)	*
FP$_{03-1}$ 24h avg [#/cm^3]	1161,2 (665-2104,4)	1129,4 (470,5-2060,1)	
FP$_{1-2.5}$ 24h avg [#/cm^3]	6,1 (3,2-9,8)	3,7 (2,2-6,2)	*
CP$_{2,5-10}$ 24h avg [#/cm^3]	2,9 (1,9-4,9)	1,3 (0,7-2,3)	*
T [°C]	25,47 (23,07-28,38)	25,89 (23,24-28,66)	n.t.

RH [%]	37,5 (34,31-43,44)	37,28 (32,44-42,54)	n.t.

Notes: [a]Only 37 night-time measurements for UFPs were available; [b]Test: Student's T test on paired data (37 paired measurements for UFPs and 140 for the other fractions) (*p < 0,05); n.t. = not tested.

4.3 HEALTH PARAMETERS

4.3.1 HRV indices

After editing, 131, 142 and 152 ambulatory ECGs were suitable for 24-hour, day-time and night-time HRV analysis respectively (< 5% ectopic beats, arrhythmic events and/or artifacts), in 79 individuals, divided in 27 "healthy" individuals, 34 with chronic ischemic heart disease, and 18 with chronic lung disease. Table 4-IV.b describes HRV measurements in the three groups.

Subjects in the three groups differed for almost all HRV indices in the time and in the frequency domains (one way ANOVA; p<0,05) (Table 4-IV.b).

Although not statistically significant, higher values of SDNN were found in healthy subjects (120.92±24.65 ms), compared with the other two groups (*Heart group* 117.22±31.81 ms and *Lung group* 110.2±31.25 ms) (Table 4-IV.b).

As summarised in Table 4-IV.b, subjects suffering from chronic ischemic heart disease showed lower heart rate values (64.9±7.16 bpm) and LF/HF ratio (3,52 ± 2,25), and higher rMSSD, PNN50, HF (both raw and normalized) values then individuals in the other groups (one way ANOVA; p<0,05). Moreover, subjects in the *Heart group* showed a wider distribution of almost all HRV indices.

Significant differences were observed between day and night periods, in almost all parameters, and in all subjects (Student's T test on paired data, p<0,05) (see Table 4-V).

Table 4-IV.a Descriptive statistics of HRV indices in the total sample (24-hour mean). **Table 4-IV.b** Differences in HRV indices among the three groups.

	Table 4-IV.a	**Table 4-IV.b**			
	Total sample	**"Healthy" Group**	**Heart Group**	**Lung Group**	**ANOVA[c]**
Subjects	75	25	33	17	
Measurements [n]	131	44	56	31	
HR 24h avg [bpm][a]	68,77 ± 7,62	70,03 ± 6,5	64,9 ± 7,16	73,96 ± 6,22	*
Time Domain					
SDNN 24h avg [ms][a]	116,8 ± 29,51	120,92 ± 24,65	117,22 ± 31,81	110,2 ± 31,25	
rMSSD 24h avg [ms][b]	24,5 (18,94 - 32,77)	21,09 (17,14 - 27,6)	30,85 (22,39 - 42,77)	22,71 (19,5 - 33,67)	*
PNN50 24h avg [ms][b]	3,61 (1,19 - 7,85)	1,97 (0,88 - 4,57)	6,63 (2,42 - 11,35)	3,08 (1,12 - 10,53)	*
SDANN 24h avg [ms][a]	100,33 ± 26,84	108,91 ± 24,48	95,09 ± 25,01	97,63 ± 30,82	*
Frequency Domain					
Total power 24h avg [ms²][b]	2488,5 (1732,75 - 3891,25)	2446 (1658,5 - 3453,5)	3023 (1863 - 4632)	2200 (1204 - 3775)	
LF/HF 24h avg[a]	4,3 ± 2,42	5,6 ± 2,14	3,52 ± 2,25	3,84 ± 2,4	*
HF 24h avg [ms²][b]	124 (65 - 201)	90,5 (60,5 - 151,5)	149 (96 - 373)	110 (65 - 207)	*
HF 24h avg [n.u.][b]	16,1 (12,22 - 25,38)	13,68 (11,07 - 16,39)	20,84 (13,49 - 31,05)	18,71 (12,65 - 26,71)	*
LF 24h avg [ms²][b]	436,5 (305 - 817,5)	395,5 (311 - 730,75)	533 (308 - 936)	426 (238 - 804)	
LF 24h avg [n.u.][b]	66,18 (57,22 - 71,49)	69,8 (65,54 - 74,65)	60,76 (51,45 - 68,01)	65,27 (49,13 - 72,32)	*
VLF 24h avg [ms²][a]	1874,97 ± 934,99	1838,8 ± 740,49	2105,89 ± 1095,68	1516,61 ± 761,45	*

Notes: [a] Data shown as mean±SD; [b] Data shown as median (25th -75th)]; [c] Test: one way ANOVA (*p < 0.05).

Table 4-V Differences in HRV indices during day and night period, in each group.

	"Healthy" Group			Heart Group			Lung Group		
	Day	Night	Test[c]	Day	Night	Test[c]	Day	Night	Test[c]
Subjects [n]	26	27		34	34		17	18	
Measurements [n]	47	51		64	66		31	35	
HR [bpm][a]	73,49 ± 6,77	61,66 ± 6,19	*	66,73 ± 8,02	60,47 ± 7,09	*	77,15 ± 7,08	65,31 ± 6,05	*
Time Domain									
SDNN [ms][a]	99,84 ± 18,43	92,05 ± 23,66	*	109,89 ± 31,78	102,37 ± 39,83	*	92,99 ± 22,87	82,67 ± 28,14	*
rMSSD [ms][b]	19,49 (15,32 - 24,57)	25,94 (18,25 - 35,33)	*	28,66 (21,75 - 45,19)	33,76 (22,98 - 48,58)	*	20,76 (17,94 - 30,28)	28,54 (20,61 - 42,49)	*
PNN50 [ms][b]	1,32 (0,48 - 3,9)	3,32 (0,93 - 10,99)	*	4,61 (1,96 - 12,29)	5,94 (2,59 - 19,79)	*	1,84 (1,03 - 7,7)	4,78 (1,37 - 19,33)	*
SDANN [ms][a]	85,56 ± 17,45	66,63 ± 21,54	*	88,64 ± 26,4	66,31 ± 23,76	*	80,72 ± 22,33	53,25 ± 17,4	*
Frequency Domain									
Total power [ms²][b]	2408 (1473 - 2885)	2412 (1712 - 4520)	*	2554 (1748- 4385)	3315,5 (1869 - 5867)	*	1935 (1261 - 2720)	2971 1320 - 4318)	*
LF/HF[a]	6,25 ± 2,65	4,75 ± 2,92	*	3,37 ± 2,19	3,5 ± 2,6		4,07 ± 2,44	3,66 ± 2,83	
HF [ms²][b]	76 (46 - 126)	112 (68 - 285)	*	149 (75 - 376)	208 (84 – 608)	*	84 (56 - 166)	182 (63 - 301)	*
HF [n.u.][b]	12,11 (9,33 - 15,42)	17,19 (11,98 - 23,84)	*	21,21 (12,92 - 31,68)	21,9 (15,65 - 33,55)	*	16,48 (12,26 - 22,14)	20,45 (14,85 - 31,06)	
LF [ms²][b]	417 (290 - 636)	412 (311 - 900)	*	423 (280 - 781)	646 (335 - 1466)	*	381 (206 - 632)	557 (235 - 816)	*
LF [n.u.][b]	69,01 (65,26 - 74,91)	70,98 (64,17 - 74,74)		60,44 (48,17 - 66,23)	61,19 (54,86 - 71,31)	*	64,03 (48,81 - 70,62)	66,9 (47,67 - 74,15)	
VLF [ms²][a]	1579 (1015 - 2054)	1804 (1252 - 3020)	*	1570 (1163- 2765)	2010 (1344 - 3803)	*	1263 (688 - 1738)	1853 (938 - 2871)	*

Notes: [a] Data shown as mean±SD; [b] Data shown as median (25th -75th)]; [c] Test: Student's T test on paired data (46, 64 and 31 measurements in the "Healthy", Heart and Lung Group respectively) (*$p < 0.05$).

4.3.2 QT period.

After editing, 128, 139 and 148 ambulatory ECGs were suitable for 24-hour, day-time and night-time QTec period measurement (< 5% ectopic beats, arrhythmic events and/or artifacts and QT period assessed by the software), in 76 individuals, 26 "healthy" individuals, 32 with chronic ischemic heart disease, and 18 with chronic lung disease.

Healthy individuals showed shorter QTec period (429.36±23.61 ms) than other subjects (one way ANOVA; p<0,05) (Table 4-VI).

Table 4-VI.a Descriptive statistics of QT period in the total sample (24-hour mean). **Table 4-VI.b** Differences in HRV indices among the three groups.

	Table 4-VI.a	Table 4-VI.b			
	Total sample	**"Healthy" Group**	**Heart Group**	**Lung Group**	**ANOVA[a]**
	mean±SD	mean±SD	mean±SD	mean±SD	
Subjects [n]	74	26	30	18	
Measurements [n]	128	42	56	30	
QTec [ms]	433,16 ± 24,45	429,36 ± 23,61	430,73 ± 25,82	443,03 ± 20,78	*

Notes: [a] Test: one way ANOVA (* = p < 0.05).

4.4 *Association between Exposure and Health Effects*

The percent change in HRV indices and QTec associated with an inter-quartile range (IQR) increase in UFPs, PM1, $PM_{2.5}$ and PM_{10}, $FP_{0.3\text{-}1}$, $FP_{1\text{-}2.5}$ and $CP_{2.5\text{-}10}$ was calculated in multivariate mixed effects models for repeated measures. Final models included age, gender, BMI, group, β-blockers, anti-hypertensive drugs (angiotensin-converting enzyme inhibitors, calcium channel blockers and diuretics drugs), alcohol consumption, high sensitivity C reactive protein and meteorological variables (temperature and relative humidity) as potential confounders.

All analyses were conducted first in the full dataset and then by group, to assess differences in effects due to health conditions. For HRV indices the same protocol was repeated, once stratified for high or low levels of hsCRP, to assess the potential influence of inflammatory status in the autonomic response to PM. The median value of hsCRP levels observed in investigated subjects was considered as cut-off (1,95 mg/L).

In the following paragraphs the most relevant results are summarised; complete results are reported in the "Annex 1 – Complete results of association between exposure and health effects".

4.4.1 Association between PM exposure and HRV indices

Association between 24-hours exposure to particles and 24-hours HRV indices

All subjects

The most relevant results of the associations between 24-hours exposure to particles and 24-hours HRV indices are summarised in Table 4-VII; complete results are reported in Table 8-I and Table 8-II of "Annex 1".

In the 24-hour period, a positive association was observed between $FP_{0.3-1}$ levels period and heart rate values in all subjects (percent change 1.4% (95% C.I. 0,01 to 2,7)) and in healthy subjects (1.9% (95% C.I. 0,01 to 3,7)) (Table 4-VII).

Table 4-VII Percent changes in 24-hour time domain HRV indices associated with an interquartile range increase in 24-hour particles exposure.

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	PM parameter	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	75	25	33	17
HR [bpm]	FP_{03-1} [#/cm^3]	**1,4 (0,01 to 2,7)***	**1,9 (0,01 to 3,7)***	1,1 (-1,1 to 3,3)	0,9 (-1,3 to 3,2)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with higher than 1,95 mg/L hsCRP

The most involved particles in the modification of HRV indices in subjects with higher than 1,95 mg/L hsCRP levels were UFPs, $FP_{0,3-1}$, $PM_{2.5}$ and PM_{10}, as summarised in Table 4-VIII; complete results are reported in Table 8-III and Table 8-IV of "Annex 1 ".

The positive association between heart rate and $FP_{0.3-1}$ was confirmed in subjects with higher hsCRP levels (percent change +2,6% (95% C.I. 0,4 to 4,9)), along with a negative association between this PM fraction and SDNN (percent change -4,4% (95% C.I. -9,2 to 0,3)) (Table 4-VIII). Moreover UFPs and $FP_{0.3-1}$ showed an association with LF/HF ratio (+29% (95% C.I. 8 to 50) and +22% (95% C.I. 4 to 39), respectively).

Once subjects with higher hsCRP levels were stratified by group, only in healthy subjects the trends observed in HRV indices in the total sample for exposure to particles to $FP_{0,3-1}$ was confirmed, with similar or stronger magnitude in the response (Table 4-VIII).

Table 4-VIII Percent changes in 24-hour time domain HRV indices associated with an interquartile range increase in 24-hour particles exposure in subjects with high hsCRP levels (hsCRP > 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
HR [bpm]	$FP_{0,3-1}$ [#/cm³]	**2,6 (0,4 to 4,9)***	**2,5 (0,01 to 4,9)***	3,9 (-3,6 to 11,3)	3,1 (-0,6 to 6,8)
SDNN [ms]	$FP_{0,3-1}$ [#/cm³]	**-4,4 (-9,2 to 0,3)°**	**-5,2 (-10,2 to -0,1)***	4,6 (-10,7 to 20)	-3,6 (-11,4 to 4,2)
LF/HF	UFPs [#/cm³]	**29,02 (8,06 to 49,98)***	**47,65 (24,89 to 70,42)***	11,43 (-17,87 to 40,73)	-29,79 (-72,56 to 12,98)
	$FP_{0,3-1}$ [#/cm³]	**21,89 (4,02 to 39,76)***	**31,65 (13,17 to 50,13)***	-6,63 (-40,96 to 27,7)	3,71 (-23,99 to 31,4)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

<u>Subjects with lower than 1,95 mg/L hsCRP</u>

The most relevant results of the associations between 24-hours exposure to particles and 24-hours HRV indices in subjects with lower than 1,95 mg/L hsCRP levels are summarised in Table 4-IX; complete results are reported in Table 8-V and Table 8-VI of "Annex 1 ".

In the total sample of subjects with lower than 1,95 mg/L hsCRP levels a significant decrease in LF/HF ratio of about -10% associated to an IQR increase in $PM_{2.5}$, PM_{10} and $FP_{0,3-1}$ was observed, due to a parallel significant increase in the denominator (high frequencies) of about 6%. A similar, but stronger, trend was confirmed in healthy subjects (about -22% for LF/HF and +11% for HF ms^2). The magnitude of response was for PM_{10} > $PM_{2.5}$ > $FP_{0,3-1}$ (Table 4-IX).

Table 4-IX Percent changes in 24-hour HRV indices associated with an interquartile range increase in 24-hour particles exposure in subjects with low hsCRP levels (hsCRP < 1,95 mg/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	35	12	16	7
LF/HF	$PM_{2,5}$ [μg/m³]	**-10,64 (-19,39 to -1,9)***	**-22,56 (-34,95 to - 10,17)***	-2,3 (-13,19 to 8,58)	-10,78 (-25,31 to 3,76)
	PM_{10} [μg/m³]	**-10,8 (-19,68 to -1,92)***	**-25,09 (-38,93 to -11,26)***	-1,88 (-13 to 9,25)	-11,82 (-27,07 to 3,44)
	$FP_{0,3-1}$ [#/cm³]	**-9,8 (-17,05 to -2,55)***	**-20,24 (-30,64 to -9,85)***	-4,22 (-13,85 to 5,41)	-6,26 (-18,27 to 5,75)
HF [n.u.]	PM_1 [μg/m³]	**7,02 (0,4 to 14,08)***	**11,38 (1,32 to 22,45)***	5,86 (-3,21 to 15,78)	2,79 (-8,86 to 15,93)
	$PM_{2,5}$ [μg/m³]	**6,95 (0,59 to 13,72)***	**11,74 (1,6 to 22,88)***	6,01 (-2,72 to 15,51)	2,84 (-8,03 to 14,99)
	PM_{10} [μg/m³]	**6,95 (0,5 to 13,81)***	**13,04 (1,68 to 25,66)***	5,36 (-3,47 to 15,01)	3,06 (-8,32 to 15,85)
	$FP_{0,3-1}$ [#/cm³]	**5,7 (0,4 to 11,1)***	**9,4 (1,2 to 17,7)***	5,2 (-2,6 to 13,1)	2 (-7,4 to 11,5)
	$FP_{1-2.5}$ [#/cm³]	**5,6 (-0,4 to 11,6)°**	**9,6 (-0,6 to 19,9)°**	5 (-3,1 to 13,2)	0,7 (-10,9 to 12,4)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

In the totality of subjects, and once subjects by low and high hsCRP levels were divided, no association was detected in the subjects suffering from chronic ischemic heart disease and from chronic lung disease. Moreover, no association was detected between $PM_{2.5-10}$ fraction and HRV indices.

Association between daily exposure to particles and daily HRV indices

<u>All subjects</u>

The most important results of mixed models fitted with daily exposure and HRV parameters are summarised in Table 4-X; complete results are reported in Table 8-VII of "Annex 1 ".

As in 24-hour data, an association between an IQR increase in $FP_{0,3-1}$and HR was detected in the total sample (percent change of +1,77 (95% C.I. 0,35 to 3,19)) and, once stratified by group, in healthy subjects (+2,19 (95% C.I. 0,27 to 4,1)). Moreover, a negative association between coarse particles and LF was observed in the total sample, but not when stratification by group was done (Table 4-X).

Table 4-X Percent changes in day HRV indices associated with an interquartile range increase in daily particles exposure.

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	77	26	34	17
HR [bpm]	$FP_{0,3-1}$ [#/cm³]	**1,77 (0,35 to 3,19)***	**2,19 (0,27 to 4,1)***	1,42 (-0,97 to 3,81)	1,38 (-1,26 to 4,02)
LF n.u.	$CP_{2,5-10}$ [#/cm³]	**-3,74 (-6,69 to -0,7)***	-4,08 (-8,69 to 0,77)	-3,48 (-8,21 to 1,49)	-3,58 (-9,71 to 2,97)
VLF [ms²]	FP_{03-1} [#/cm³]	**-12,33 (-21,92 to -2,74)***	**-13,56 (-26,6 to -0,53)***	-11,92 (-27,6 to 3,76)	-10,18 (-28,57 to 8,21)
	$FP_{1-2.5}$ [#/cm³]	**-13,06 (-23,35 to -2,77)***	-12,53 (-27,6 to 2,54)	-13,69 (-29,46 to 2,07)	-12,95 (-32,29 to 6,39)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with higher than 1,95 mg/L hsCRP

Results of the associations between daily exposure to particles and daily HRV indices in subjects with higher than 1,95 mg/L hsCRP levels are summarised in Table 4-XI; complete results are reported in Table 8-VIII of "Annex 1". In subjects with higher levels of hsCRP, daily HRV changes were mainly due to exposure to $CP_{2.5-10}$: a decrease in LF/HF (about -10%), along with an increase in HF (and other vagal indices, i.e. rMSSD and PNN50) and a decrease in LF was observed in association with an increase in this fraction (Table 4-XI). Once analysis by group was performed, these finding were confirmed in healthy subjects only (Table 4-XI).

Table 4-XI Percent changes in day HRV indices associated with an interquartile range increase in daily particles exposure in subjects with high hsCRP levels (hsCRP > 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV	**PM**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)

index	parameter				
	Subjects [n]	40	13	17	10
rMSSD [ms]	$CP_{2,5\text{-}10}$ [#/cm³]	**13,4 (3,25 to 24,54)***	**22,72 (6,7 to 41,15)***	11,9 (-7,15 to 34,87)	4,08 (-11,88 to 22,93)
PNN50 [%]	$CP_{2,5\text{-}10}$ [#/cm³]	**37,18 (7,86 to 74,47)***	**53,42 (5,46 to 123,17)***	31,41 (-19,3 to 114)	22,64 (-21,71 to 92,13)
LF/HF	$CP_{2,5\text{-}10}$ [#/cm³]	**-10,66 (-19,8 to -1,53)***	**-15,94 (-29,95 to -1,93)***	-2,88 (-21,8 to 16,03)	-11,19 (-27,8 to 5,42)
HF [ms²]	$CP_{2,5\text{-}10}$ [#/cm³]	**27,74 (6,29 to 53,51)***	**39,4 (5,1 to 84,89)***	31,34 (-10,01 to 91,69)	10,3 (-21,15 to 54,3)
HF n.u.	$CP_{2,5\text{-}10}$ [#/cm³]	**13,34 (4,51 to 22,91)***	**17,32 (3,46 to 33,05)***	11,75 (-5,54 to 32,22)	9,7 (-5,53 to 27,4)
LF n.u.	$CP_{2,5\text{-}10}$ [#/cm³]	**-7,13 (-12,17 to -1,8)***	**-10,23 (-17,7 to -2,09)***	-0,04 (-11,18 to 12,51)	-8,77 (-17,68 to 1,1)
VLF [ms²]	$FP_{1\text{-}2.5}$ [#/cm³]	**-8,42 (-15,37 to -1,46)***	-6,1 (-14,13 to 1,93)	-14,56 (-33,89 to 4,77)	**-12,96 (-26,01 to 0,08)°**

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with lower than 1,95 mg/L hsCRP

In subjects with low hsCRP levels, no statistically significant association was detected between daily exposure levels and HRV indices. Complete results are reported in Table 8-IX of "Annex 1".

Association between night-time exposure to particles and night-time HRV indices

Due to technical reasons only 37 night-time measurement of UFPs were available for analysis; due to this small sample size, the mixed model could not be fitted for this data.

All subjects

During the night period, the most important association observed was the one between exposure to $FP_{0,3\text{-}1}$ and SDNN in the total sample (percent change -5,69% (95% C.I -10,76 to -0,62)) and in the *Heart group* subjects although the latter did not achieve statistical significance (-8,61%; p = 0,063) (Table 4-XII). Other statistically significant results of the associations between night-time exposure to particles and night-time HRV indices are summarised in Table 4-XII and complete results are reported in Table 8-X of "Annex 1".

Table 4-XII Percent changes in night-time HRV indices associated with an interquartile range increase in night-time particles exposure.

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	79	27	34	18
SDNN [ms]	FP_{03-1} [#/cm³]	**-5,69 (-10,76 to -0,62)***	-4,28 (-10,52 to 1,96)	**-8,61 (-17,57 to 0,35)°**	-6,3 (-15,82 to 3,22)
SDANN [ms]	FP_{03-1} [#/cm³]	**-6,6 (-13,18 to -0,02)***	-5,06 (-13,34 to 3,21)	-8,78 (-20 to 2,44)	-8,17 (-21,46 to 5,11)
LF n.u.	$CP_{2,5-10}$ [#/cm³]	**-5,76 (-9,61 to -1,75)***	-1,57 (-8,43 to 5,81)	**-8,85 (-14,32 to -3,04)***	-5,45 (-13,2 to 3)
VLF [ms²]	FP_{03-1} [#/cm³]	**-18,77 (-35,55 to -2)***	-14,75 (-35,79 to 6,29)	**-30,7 (-59,09 to -2,31)***	-13 (-46,95 to 20,95)

Notes: [a] Insufficient UFPs night-time data for analysis *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with higher than 1,95 mg/L hsCRP

Results of the associations between night-time exposure to particles and night-time HRV indices in subjects with higher than 1,95 mg/L hsCRP levels are summarised in Table 4-XIII; complete results are reported in Table 8-XI of "Annex 1".

The most relevant finding was an increase in the LF/HF ratio associated to exposure to $FP_{0,3-1}$ in all subjects. This association was confirmed in healthy subjects with high levels of hsCRP only (Table 4-XIII).

Table 4-XIII Percent changes in night-time HRV indices associated with an interquartile range increase in night-time particles exposure in subjects with high hsCRP levels (hsCRP > 1,95 mg/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
SDANN [ms]	FP_{03-1} [#/cm³]	**-11,49 (-22,46 to -0,52)***	-10,03 (-22,19 to 2,14)	-12,07 (-36,24 to 12,1)	-18,31 (-39,46 to 2,83)
LF/HF	FP_{03-1} [#/cm³]	**22,42 (2,95 to 41,89)***	**33,26 (12,33 to 54,19)***	0,35 (-40,25 to 40,94)	-14,35 (-50,43-21,73)

Notes: [a] Insufficient UFPs night-time data for analysis *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with lower than 1,95 mg/L hsCRP

Results of the associations between night-time exposure to particles and night-time HRV indices in subjects with lower than 1,95 mg/L hsCRP levels are summarised in Table 4-XIV; complete results are reported in Table 8-XII of "Annex 1".

A decrease in the LF/HF ratio was observed in the total sample in association to fine particles in the accumulation mode and $FP_{1-2,5}$, being the former six-fold more strongly associated than the latter (-20,41% (95% C.I. -35,29 to -5,52) and -3,17 (95% C.I. -5,33 to -1). This decrease in the LF/HF ratio was due to both an increase in the denominator and a decrease in the numerator. The same trends in the effects of particles, i.e. a larger effects of $FP_{0,3-1}$ than $FP_{1-2,5}$, were observed in association with HF. These findings were confirmed in the *"Healthy" group*, except for the decrease in LF that was found in the *Heart group* only (Table 4-XIV).

Table 4-XIV Percent changes in night-time HRV indices associated with an interquartile range increase in night-time particles exposure in subjects with low hsCRP levels (hsCRP < 1,95 mg/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	39	14	17	8
LF/HF	FP_{03-1} [#/cm³]	**-20,41 (-35,29 to -5,52)***	**-28,69 (-47,46 to -9,91)***	-8,53 (-32,65 to 15,6)	-12,74 (-44,77 to 19,3)
	$FP_{1-2.5}$ [#/cm³]	**-3,17 (-5,33 to -1)***	**-3,88 (-6,8 to -0,96)***	-3,4 (-7,14 to 0,35)	1,34 (-4 to 6,68)
HF n.u.	FP_{03-1} [#/cm³]	**12,21 (2,67 to 22,64)***	**15,43 (3,09 to 29,25)***	11,87 (-3,42 to 29,59)	3,84 (-13,97 to 25,34)
	$FP_{1-2.5}$ [#/cm³]	**7,09 (0,12 to 14,55)***	**10,05 (0,57 to 20,42)***	7,09 (-4,79 to 20,46)	-5,62 (-19,93 to 11,26)
LF n.u.	$FP_{1-2.5}$ [#/cm³]	**-3,63 (-6,75 to -0,41)***	-3,98 (-8,1-0,34)	**-5,46 (-10,71 to 0,09)°**	2,42 (-5,48 to 10,98)

Notes: [a] Insufficient UFPs night-time data for analysis *p < 0,05; °Borderline statistical significance (p < 0,07).

Association between daily exposure to particles and night-time HRV indices

<u>All subjects</u>

Results of the associations between night-time exposure to particles and night-time HRV indices are summarised in Table 4-XV; complete results are reported in Table 8-XIII of "Annex 1".

In the night period a negative association was found between exposure to fine particles in the accumulation mode ($FP_{0,3-1}$) and SDNN. This finding was confirmed in all studied groups with a magnitude of response that was *Lung group* > *Heart group* > *"Healthy" group*. SDANN and VLF was also negatively associated with exposure to $FP_{0,3-1}$ in the total sample, but the relationship was not found once stratification for group was performed. Moreover, in the totality of subjects a decrease in LF n.u. and in VLF was found in association with coarse particles and ultrafine particles respectively; this association was confirmed in subjects suffering from chronic ischemic heart disease only (Table 4-XV).

Table 4-XV Percent changes in night-time HRV indices associated with an interquartile range increase in daily particles exposure.

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	79	27	34	18
SDNN [ms]	FP_{03-1} [#/cm³]	**-7,88 (-12,67 to -3,1)***	**-6,77 (-13,41 to -0,13)***	**-8,36 (-16,22 to -0,49)***	**-9,08 (-17,18 to -0,98)***
SDANN [ms]	FP_{03-1} [#/cm³]	**-8,62 (-15,06 to -2,18)***	-8,19 (-17,14 to 0,75)	-8,52 (-18,97 to 1,93)	-9,46 (-20,81 to 1,88)
LF n.u.	$CP_{2,5-10}$ [#/cm³]	**-4,43 (-7,85 to -0,88)***	-4,22 (-9,94 to 1,86)	**-7,4 (-12,69 to -1,79)***	-0,26 (-6,83 to 6,76)
VLF [ms²]	UFPs [#/cm³]	**-23,02 (-42,96 to -3,09)***	-16,56 (-48,88 to 15,77)	**-29,93 (-55,09 to -4,77)***	-7,84 (-55,7 to 40,01)
	FP_{03-1} [#/cm³]	**-21,8 (-38,57 to -5,03)***	-21,52 (-44,8 to 1,76)	-22,69 (-49,8 to 4,42)	-21,19 (-51,06 to 8,69)
	$FP_{1-2.5}$ [#/cm³]	**-17,71 (-34,68 to -0,75)***	-16,77 (-43,22 to 9,68)	-18,4 (-45,5 to 8,69)	-18,12 (-46,42 to 10,18)

Notes: * = $p < 0,05$; ° = statistical significance borderline, $p < 0,07$

<u>Subjects with higher than 1,95 mg/L hsCRP</u>

The only significant results when the associations between night-time exposure to particles and night-time HRV indices in subjects with higher hsCRP levels were assessed was a negative association between VLF and UFPs exposure, that was observed in the total sample and confirmed only in the *Heart group* (Table 4-XVI). Complete results are reported in Table 8-XIV of "Annex 1".

Table 4-XVI Percent changes in night-time HRV indices associated with an interquartile range increase in daily particles exposure in subjects with high hsCRP levels (hsCRP > 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
VLF [ms²]	UFPs [#/cm³]	**-25,88 (-51,62 to -0,13)***	-23,8 (-65,71 to 18,1)	**-34,31 (-67,57 to -1,06)***	-5,05 (-60,43 to 50,34)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

Subjects with lower than 1,95 mg/L hsCRP

Results of the associations between daily exposure to particles and night-time HRV indices in subjects with lower than 1,95 mg/L hsCRP levels are summarised in Table 4-XVII; complete results are reported in Table 8-XV of "Annex 1".

A decrease of SDNN was associated with an IQR increase in $FP_{0,3-1}$ (percent change -10,35% (95% C.I. -19,56 to -1,14)), $FP_{1-2,5}$ (-11,04% (95% C.I. -20,51 to-1,56)) and coarse particles (-7,27%, p = 0.068) in the total group, and confirmed only for $FP_{1-2,5}$ in the *Lung group*. Also, the negative association between SDANN and $FP_{1-2,5}$ was confirmed only in the *Lung group* only (Table 4-XVII).

Moreover, a decrease in the LF/HF ratio, associated to an increase in high frequency values, was related to fine particles (both $FP_{0,3-1}$ and $FP_{1-2,5}$) in the total group. Once stratified by group, the same results were found in healthy subjects and in subjects suffering from chronic ischemic heart disease (only for $FP_{1-2,5}$ in the latter case) (Table 4-VII).

Table 4-XVII Percent changes in night-time HRV indices associated with an interquartile range increase in daily particles exposure in subjects with low hsCRP levels (hsCRP < 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
HRV index	**PM parameter**	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	39	14	17	8
SDNN [ms]	FP_{03-1} [#/cm³]	**-10,35 (-19,56 to -1,14)***	-8,79 (-25,09 to 7,52)	-9,53 (-21,83 to 2,77)	-14,21 (-33,19 to 4,77)
	$FP_{1-2.5}$ [#/cm³]	**-11,04 (-20,51 to-1,56)***	-6,7 (-23,6 to 10,2)	-7,48 (-19,9 to 4,94)	**-23 (-40,2 to -5,8)***

	$CP_{2,5-10}$ [#/cm^3]	**-7,27 (-15,09 to 0,55)°**	-3,75 (-21,46 to 13,96)	-8,45 (-18,88 to 1,98)	-7,12 (-23,73 to 9,5)
SDANN [ms]	$FP_{1-2.5}$ [#/cm^3]	**-12,52 (-24,23 to -0,82)***	-8,18 (-29,03 to 12,67)	-10,14 (-25,76 to 5,49)	**-22,05 (-43,64 to -0,46)***
LF/HF	FP_{03-1} [#/cm^3]	**-22,72 (-39,91 to -5,54)***	**-55,54 (-82,17 to -28,91)***	-11,66 (-32,81 to 9,49)	-15,42 (-45,33 to 14,48)
	$FP_{1-2.5}$ [#/cm^3]	**-4,27 (-7,55 to -1)***	**-6,84 (-12,91 to -0,77)***	**-4,55 (-8,99 to -0,12)***	-1,03 (-7,03 to 4,98)
HF n.u.	FP_{03-1} [#/cm^3]	**13,87 (2,96 to 25,93)***	**27,32 (7,65 to 50,59)***	11,76 (-2,11 to 27,59)	6,46 (-11,62 to 28,23)
	$FP_{1-2.5}$ [#/cm^3]	**14,29 (3,67 to 26)***	**23,49 (3,17 to 47,8)***	**14,96 (0,81 to 31,09)***	4,52 (-12,51to 24,87)
VLF [ms^2]	$FP_{1-2.5}$ [#/cm^3]	**-19,49 (-35,93 to -3,04)***	-2,29 (-31,16 to 26,58)	-18,48 (-39,67 to 2,71)	**-37,74 (-67,09 to -8,4)***
	$CP_{2,5-10}$ [#/cm^3]	**-14,22 (-27,59 to -0,85)***	5,52 (-24,33 to 35,36)	**-21,01 (-38,41 to -3,6)***	-13,02 (-40,79 to 14,76)

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

4.4.2 Association between PM exposure and QT period

No statistically significant association was observed in the total sample between exposure to particles and QTec period, neither in the 24-hour period or during the day or the night period, nor when daily exposure was associated with night-time QTec data (Table 4-XVIII). Due to this lack of association in the total sample, no stratification for group was performed.

Table 4-XVIII Percent changes in QTec period associated with an interquartile range increase in particles exposure in the total sample.

	24h exposure vs. 24h Qtec	**Daily exposure vs. Daily QTec**	**Night-time exposure vs. Night-time QTec**	**Daily exposure vs. Night-time QTec**
	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
Subjects [n]	74	76	78	78
UFPs [#/cm^3]	-0,37 (-1,57 to 0,83)	0,21 (-0,96 to 1,38)	-[a]	0,17 (-1,01 to 1,34)
PM_1 [μg/m^3]	-0,56 (-1,55 to 0,42)	-	-	-
$PM_{2,5}$ [μg/m^3]	-1,38 (-6,29 to 3,52)	-	-	-
$PM_{2,5-10}$ [μg/m^3]	-0,11 (-0,3 to 0,08)	-	-	-
PM_{10} [μg/m^3]	0 (-0,02 to 0,02)	-	-	-
FP_{03-1} [#/cm^3]	68,67 (-497,58 to 634,92)	0,26 (-0,61 to 1,14)	-0,22 (-1,12 to 0,69)	0,1 (-0,98 to 1,19)
$FP_{1-2.5}$ [#/cm^3]	0 (0 to 0,01)	0,21 (-1,25 to 1,67)	-0,95 (-4,76 to 2,87)	0,02 (-1,08 to 1,11)
$CP_{2,5-10}$ [#/cm^3]	-0,37 (-1,57 to 0,83)	0 (0 to 0,04)	-0,1 (-0,2 to 0,08)	0,12 (-0,9 to 1,1)

Notes: [a] Insufficient UFPs night-time data for analysis; *p < 0,05.

5 DISCUSSION

A great number of epidemiological studies have demonstrated the association between particulate air pollution and cardiovascular morbidity and mortality; some subpopulations seem to be more susceptible, e.g individual with pre-existing cardiac or pulmonary disease[7, 8]. Air pollution has been associated with ventricular arrhythmias, implantable defibrillator discharges, atrial fibrillation and ECG repolarization abnormalities[12, 58, 100-104]. In agreement with these observations, a sizeable portion of the CV morbidity and mortality stemming from PM exposure has been shown to be due to cardiac arrhythmias and sudden death[1, 4, 101, 105, 106]. The responsible mechanism is likely to be that the inhalation of particles into the pulmonary tree i) can alter neural reflexes, which then disrupt cardiac autonomic balance and lead to myocardial electrical instability[107]; ii) might exacerbate the autonomic function of the heart via induced inflammation in lung and pro-inflammatory cytokine expression in cardiac macrophages[9]. Previous observations have demonstrated that patients with reduced capacities to defend against oxidative stress (e.g. a glutathione S-transferaseM1 polymorphism) have a more robust alteration in HRV[74, 80, 84]. This is important as it further demonstrates the central role of 'oxidative stress' as a fundamental core pathway whereby PM imparts biological harm. The role of the inflammation for the autonomic effects of particles is less defined.

In this study the association between individual exposure to particles of different size, indices of autonomic control of heart rhythm, i.e. heart rate variability, and arrhythmic proneness (QT period) was assessed in subjects suffering from chronic ischemic heart disease or chronic lung disease (COPD or asthma) and without the afore mentioned diseases, taking into account the role of the inflammatory status.

A predominance of the male gender was studied in particular in subjects with chronic ischemic heart disease, due to the epidemiological characteristics of cardiovascular disease[108]. In this group, almost all subjects were under antihypertensive treatment. As expected, in healthy subjects drug assumption was less important, although not absent, and in this group a small amount of subjects was found suffering from hypertension and dyslipidemia. In subjects suffering from chronic lung disease more than half were under treatment with long acting β_2-agonist, and almost half used antihypertensive drugs. It should be said that both β-blockers and long acting β_2-agonist, but also calcium channels antagonist and ACE-inhibitors can influence the autonomic control of heart rhythm[93].

Investigated subjects experienced high levels of exposure to $PM_{2.5}$ and PM_{10}. In particular, exposure to $PM_{2.5}$ exceeded the 24-hour mean of 25 $\mu g/m^3$ suggested by WHO in both the investigated periods, i.e. Summer and Winter, while the limit suggested for PM_{10} (i.e. 50 $\mu g/m^3$) was exceeded only in Winter[109]. Observed PM_{10} concentrations were similar to twenty four hours average reported for urban background in Europe[110], and $PM_{2.5}$ concentrations were similar to the previously reported for personal monitoring indoor and outdoor in Milan[20]. Moreover, UFPs levels could be considered in the high range, given that number concentration of particles smaller than 100 nm in urban background environments can range from a few thousand to some 20.000 particles per cm^3[109, 111]. As expected, higher levels of exposure to almost all particles were observed in the cold season and during day time, except for levels of exposure to fine particles in the accumulation mode ($FP_{0,3-1}$), that was comparable during the day and the night period.

Significantly decrease in SDNN, that reflects all cyclic components responsible for variability of heart in the period of recording (e.g. sympathetic and vagal modulation of heart rate), has been reported for subjects suffering from chronic ischemic heart disease[93] or chronic lung disease[112, 113]. SDNN values observed in the present study were lower in subjects suffering from these diseases than in healthy individuals, although differences were not statistically significant. This lack of significance could be due to drug use in non-healthy subjects that could influence HRV (e.g. β-adrenergic antagonist[114, 115] or long acting β_2 agonist[93]). Vagal indices (rMSSD, PNN50 and HF) in healthy subjects fell within the normal range, whereas higher and wider distributed values was observed in the *Heart* and *Lung* groups for these parameters, probably due to the health condition and the drug treatment[93]. Circadian rhythm of HRV indices was preserved in all groups, with a prevalence of vagal indices during the night period. QT period values were in the normal range in the three groups of subjects.

The relationship between decreases in HRV and increased cardiac mortality rate is well established in patients with a wide spectrum of cardiac disorders[93], including those with left ventricular dysfunction and congestive heart failure[116, 117], those who have recently had a myocardial infarction [118], those with stable coronary disease[93], and even survivors of sudden cardiac death not associated with coronary disease[119]. The predictive value of HRV for death and arrhythmic complications is independent of other risk stratification factors such as depressed left ventricular ejection fraction, increased ventricular ectopic activity, or the presence of ventricular late potentials[93]. The direction of alterations in the whole heart rate variability (SDNN) in response to higher levels of particles observed in the present study are the same as those associated with increased cardiac mortality rate. A decrease in SDNN was observed for an increase in particles in the accumulation mode. This association was evident during night-time in the total population and was confirmed only in subjects with chronic ischemic heart disease (CHD). A greater decrease was seen when a lag of approximately 12 hours was considered (i.e. daily exposure to particles versus night-time SDNN), concerning all investigated groups, that was suggestive of an increase of response over time in CHD subjects and a delayed effect in subjects without CHD, although it should not be excluded that this stronger association could be due to the higher stability of HRV indices during night-time[93]. Along with SDNN, also a decrease was observed in the low frequency power of the HRV spectrum, an index of sympathetic mediators that appear to exert their influence over longer time periods[120, 121] and the very low frequency, whose interpretation is less defined[93].

Which fraction of particulate matter is the most harmful is still unknown (see Table 1-I). Generally, a decrease in HRV has been associated with an increase in fine particles[46, 60, 62, 64, 67, 72-75, 78-82, 84-87]. When effects of both coarse and fine particles on HRV indices were investigated, controversial results were obtained. Gold et al.[46], Creason et al.[63] and Adar et al.[78] observed changes in HRV indices associated only with the fine fraction. On the other hand, coarse but not fine particles were demonstrated to decrease HRV in adults with CAD[76], or in subjects with lung disease[71, 83]. Results in the present study suggest that the inflammatory status, as defined by hsCRP levels, could play an important role in susceptibility to different particles fraction. The effects of coarse particles on vagal tone could somehow be connected with inflammatory mechanisms, as indicated by the positive association between the exposure to coarse particles and the indices of vagal modulation of heart rhythm (i.e. rMSSD, PNN50 and high frequency), that was observed during day-time in healthy subjects with higher levels of hsCRP. These findings were not confirmed either during night-time or when the 12 hours lag time was considered, indicating a shorter and more acute effect of coarse particles and the need for higher concentration to an effect to be observed, given that the daily concentrations were found to be higher than those during night-time. On the other hand, the association between heart rate variability and fine particles seems to be independent from inflammatory mechanisms, as indicated by results in subjects with lower levels of hsCRP. In these subjects an increase in vagal tone, i.e. HF[93], coupled to a decrease in the LF/HF ratio, was found during the 24-hour period in the total population and was confirmed only in healthy subjects. During night period even stronger associations were observed, with further prominent ones when the 12 hours lag was considered (i.e. daily exposure versus night-time), concerning prevalently healthy subjects for exposure to particles in the accumulation mode, and subjects with CHD for exposure to larger fine particles ($FP_{1\text{-}2.5}$), suggesting an increase of response over time in healthy subjects and a delayed effect in subjects with CHD, probably independent from inflammatory mechanisms.

A direct interaction of particles with CV system, in particular of translocated ultrafine particles, seems to be less involved in the autonomic dysfunction induced by particles, as suggested by the poor associations among exposure to UFPs and changes in HRV indices observed in the current study.

The associations found in this work only partially confirm those seen in past studies. However, effects of air pollutants on HRV are not entirely consistent across studies reported in literature (see Table 1-I). The decrease in total heart rate variability found in the current study are consistent with previous findings, given that many authors demonstrated a decrease in SDNN related to PM exposure[59, 62, 70, 72, 73, 80, 122]. On the other hand, only a few authors have demonstrated an increase in vagal indices related to exposure PM as in this work[45, 69, 77], with the majority of authors demonstrating a negative relationship between vagal indices and PM [59, 62, 70, 72, 73, 78, 80, 122]. Potential factors that may explain these discrepancies include age and health status of study participants[81], sources and composition of particles[65, 77, 82, 86].

A major strength of this study is the individual exposure assessment to PM fractions, including UFPs. Supersite or urban monitoring stations are generally used in studies dealing with the association between PM exposure and cardiovascular effects, although several studies reported low associations between particulate matter personal and outdoor exposure monitoring[18, 19]. A personal exposure assessment was used only in few other studies, and seldom for all PM fractions[64, 70, 78]. In particular, a small amount of studies have investigated the role of UFPs[54, 61]. An additional strength consists in repeated measures in the same subjects in different seasons.

Potential weaknesses of this study include the small sample size and the heterogeneity of health conditions and medication use within each studied group.

6 CONCLUSIONS

In conclusion, in the present study an effect of particles on autonomic regulation of heart rhythm but not an influence on QT period was demonstrated.

The observed results suggest a major role of fine particles leading to acute and delayed alteration in autonomic control of heart rhythm in healthy subjects and subjects with chronic ischemic heart disease, probably not related to inflammatory status. On the other hand, coarse particles possibly need higher concentrations to exert their effects on autonomic control of heart rhythm, and these effects could be linked to inflammatory mechanisms in healthy subjects. Ultrafine particles appear to be less involved in the observed associations.

Healthy subjects and subjects with chronic ischemic heart disease seem to be more prone to alteration of autonomic heart rate control due to exposure to particles, while subjects suffering from chronic lung disease seem to be less susceptible.

Several questions are still to be answered, including the role of pollution source (e.g. traffic) and chemical-physical characteristics, the existence of a temporal lag between the exposure and the effects, whether inflammation (perhaps in pulmonary tissue) is somehow required to trigger the neural reflex/reduced HRV, in particular for coarse particles, and whether the altered HRV is a causal mediator of events compared with an epiphenomenon and whether altered HRV actually reflects changes in central nervous system autonomic outflow.

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8 Annexes

Annex 1 – Complete results of association between exposure and health effects

TABLE 8-I PERCENT CHANGES IN 24-HOUR TIME DOMAIN HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN 24-HOUR PARTICLES EXPOSURE.

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	75	25	33	17
HR [bpm]	UFPs [#/cm³]	-0,51 (-2,33 to 1,3)			
	PM_1 [μg/m³]	1,06 (-0,61 to 2,74)			
	$PM_{2,5}$ [μg/m³]	0,98 (-0,67 to 2,62)			
	$PM_{2,5\text{-}10}$ [μg/m³]	-0,4 (-2,07 to 1,26)			
	PM_{10} [μg/m³]	0,87 (-0,88 to 2,62)			
	$FP_{03\text{-}1}$ [#/cm³]	**1,4 (0,01 to 2,7)***	**1,9 (0,01 to 3,7)***	1,1 (-1,1 to 3,3)	0,9 (-1,3 to 3,2)
	$FP_{1\text{-}2.5}$ [#/cm³]	0 (-1,5 to 1,6)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,46 (-1,84 to 0,93)			
SDNN [ms]	UFPs [#/cm³]	0,88 (-3,91 to 5,67)			
	PM_1 [μg/m³]	0,84 (-3,66 to 5,33)			
	$PM_{2,5}$ [μg/m³]	0,97 (-3,45 to 5,39)			
	$PM_{2,5\text{-}10}$ [μg/m³]	0,74 (-3,65 to 5,13)			
	PM_{10} [μg/m³]	1,09 (-3,6 to 5,78)			
	$FP_{03\text{-}1}$ [#/cm³]	-0,9 (-4,6 to 2,8)			
	$FP_{1\text{-}2.5}$ [#/cm³]	0,7 (-3,4 to 4,9)			
	$CP_{2,5\text{-}10}$ [#/cm³]	0,57 (-3,08 to 4,22)			
rMSSD [ms]	UFPs [#/cm³]	3,8 (-4,53 to 12,86)			
	PM_1 [μg/m³]	0,4 (-7,25 to 8,69)			
	$PM_{2,5}$ [μg/m³]	1,05 (-6,53 to 9,24)			
	$PM_{2,5\text{-}10}$ [μg/m³]	3,21 (-4,65 to 11,71)			
	PM_{10} [μg/m³]	1,63 (-6,46 to 10,42)			
	$FP_{03\text{-}1}$ [#/cm³]	-1,1 (-7,7 to 5,5)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-0,1 (-7,3 to 7,3)			
	$CP_{2,5\text{-}10}$ [#/cm³]	5,17 (-1,57 to 12,37)			
PNN50 [%]	UFPs [#/cm³]	7,09 (-16,78 to 37,8)			
	PM_1 [μg/m³]	-0,45 (-21,31 to 25,95)			
	$PM_{2,5}$ [μg/m³]	1,11 (-19,74 to 27,36)			
	$PM_{2,5\text{-}10}$ [μg/m³]	6,45 (-15,23 to 33,66)			
	PM_{10} [μg/m³]	2,35 (-19,86 to 30,72)			
	$FP_{03\text{-}1}$ [#/cm³]	-3,9 (-23,3 to 16)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-2,8 (-24,5 to 19,5)			
	$CP_{2,5\text{-}10}$ [#/cm³]	18,04 (-2,2 to 42,48)			

SDANN [ms]	UFPs [#/cm^3]	1,77 (-3,7 to 7,24)			
	PM_1 [µg/m^3]	2,45 (-2,67 to 7,57)			
	$PM_{2,5}$ [µg/m^3]	2,49 (-2,53 to 7,52)			
	$PM_{2,5\text{-}10}$ [µg/m^3]	2 (-2,91 to 6,91)			
	PM_{10} [µg/m^3]	2,83 (-2,49 to 8,15)			
	$FP_{03\text{-}1}$ [#/cm^3]	0,4 (-3,9 to 4,6)			
	$FP_{1\text{-}2.5}$ [#/cm^3]	2,4 (-2,4 to 7,1)			
	$CP_{2,5\text{-}10}$ [#/cm^3]	1,36 (-2,71 to 5,43)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

<u>TABLE 8-II</u> PERCENT CHANGES IN 24-HOUR FREQUENCY DOMAIN HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN 24-HOUR PARTICLES EXPOSURE.

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	75	25	33	17
TP [ms^2]	UFPs [#/cm^3]	1,16 (-8,36 to 11,68)			
	PM_1 [µg/m^3]	-0,39 (-8,65 to 8,62)			
	$PM_{2,5}$ [µg/m^3]	0,03 (-8,13 to 8,92)			
	$PM_{2,5\text{-}10}$ [µg/m^3]	-1,18 (-9,46 to 7,85)			
	PM_{10} [µg/m^3]	-0,19 (-8,83 to 9,27)			
	$FP_{03\text{-}1}$ [#/cm^3]	-2,2 (-9,4 to 5,1)			
	$FP_{1\text{-}2.5}$ [#/cm^3]	-1,7 (-9,6 to 6,3)			
	$CP_{2,5\text{-}10}$ [#/cm^3]	1,13 (-6,04 to 8,85)			
LF/HF	UFPs [#/cm^3]	6,99 (-3,52 to 17,51)			
	PM_1 [µg/m^3]	0,1 (-1,99 to 2,18)			
	$PM_{2,5}$ [µg/m^3]	4,49 (-4,63 to 13,61)			
	$PM_{2,5\text{-}10}$ [µg/m^3]	-2,98 (-12,02 to 6,07)			
	PM_{10} [µg/m^3]	3,69 (-5,99 to 13,36)			
	$FP_{03\text{-}1}$ [#/cm^3]	5,68 (-2,07 to 13,44)			
	$FP_{1\text{-}2.5}$ [#/cm^3]	-0,3 (-2,2 to 1,6)			
	$CP_{2,5\text{-}10}$ [#/cm^3]	-3,77 (-11,25 to 3,7)			
HF [ms^2]	UFPs [#/cm^3]	5,86 (-10,83 to 25,68)			
	PM_1 [µg/m^3]	2,42 (-12,04 to 19,26)			
	$PM_{2,5}$ [µg/m^3]	3,66 (-10,74 to 20,37)			
	$PM_{2,5\text{-}10}$ [µg/m^3]	4,64 (-10,26 to 22,01)			
	PM_{10} [µg/m^3]	4,42 (-10,92 to 22,41)			
	$FP_{03\text{-}1}$ [#/cm^3]	-0,8 (-13,6 to 12,1)			
	$FP_{1\text{-}2.5}$ [#/cm^3]	2,4 (-11,6 to 16,6)			

	$CP_{2,5-10}$ [#/cm³]	8,66 (-4,44 to 23,54)	
HF [n.u.]	UFPs [#/cm³]	0,2 (-7,1 to 8,07)	
	PM_1 [µg/m³]	-0,16 (-6,55 to 6,66)	
	$PM_{2,5}$ [µg/m³]	0,36 (-5,94 to 7,1)	
	$PM_{2,5-10}$ [µg/m³]	2,6 (-3,9 to 9,55)	
	PM_{10} [µg/m³]	0,84 (-5,87 to 8,03)	
	FP_{03-1} [#/cm³]	-0,7 (-6,3 to 4,9)	
	$FP_{1-2.5}$ [#/cm³]	1,2 (-4,9 to 7,4)	
	$CP_{2,5-10}$ [#/cm³]	4,27 (-1,26 to 10,1)	
LF [ms²]	UFPs [#/cm³]	6,2 (-6,89 to 21,13)	
	PM_1 [µg/m³]	3,01 (-8,4 to 15,84)	
	$PM_{2,5}$ [µg/m³]	3,42 (-7,84 to 16,06)	
	$PM_{2,5-10}$ [µg/m³]	0,11 (-11,02 to 12,63)	
	PM_{10} [µg/m³]	3,33 (-8,59 to 16,8)	
	FP_{03-1} [#/cm³]	0,5 (-9,2 to 10,4)	
	$FP_{1-2.5}$ [#/cm³]	1 (-9,8 to 11,8)	
	$CP_{2,5-10}$ [#/cm³]	2,04 (-7,52 to 12,58)	
LF [n.u.]	UFPs [#/cm³]	1,32 (-2,3 to 5,08)	
	PM_1 [µg/m³]	0,41 (-2,72 to 3,65)	
	$PM_{2,5}$ [µg/m³]	0,14 (-2,93 to 3,32)	
	$PM_{2,5-10}$ [µg/m³]	-1,67 (-4,8 to 1,55)	
	PM_{10} [µg/m³]	-0,17 (-3,44 to 3,2)	
	FP_{03-1} [#/cm³]	0,7 (-2 to 3,4)	
	$FP_{1-2.5}$ [#/cm³]	-0,1 (-3 to 2,8)	
	$CP_{2,5-10}$ [#/cm³]	-1,96 (-4,59 to 0,75)	
VLF	UFPs [#/cm³]	-0,98 (-10,23 to 8,27)	
	PM_1 [µg/m³]	-2,51 (-10,5 to 5,49)	
	$PM_{2,5}$ [µg/m³]	-2,15 (-10,01 to 5,7)	
	$PM_{2,5-10}$ [µg/m³]	-1,39 (-9,2 to 6,42)	
	PM_{10} [µg/m³]	-2,35 (-10,66 to 5,95)	
	FP_{03-1} [#/cm³]	-3,2 (-9,9 to 3,4)	
	$FP_{1-2.5}$ [#/cm³]	-4,3 (-11,7 to 3,1)	
	$CP_{2,5-10}$ [#/cm³]	-1,72 (-8,21 to 4,77)	

Notes: *$p < 0,05$; °Borderline statistical significance ($p < 0,07$).

<u>TABLE 8-III</u> PERCENT CHANGES IN 24-HOUR TIME DOMAIN HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN 24-HOUR PARTICLES EXPOSURE IN SUBJECTS WITH HIGH HSCRP LEVELS (HSCRP > 1,95 MG/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
HR [bpm]	UFPs [#/cm³]	-1,19 (-4,03 to 1,65)			
	PM_1 [µg/m³]	2,25 (-0,38 to 4,88)			
	$PM_{2,5}$ [µg/m³]	2,12 (-0,52 to 4,75)			
	$PM_{2,5\text{-}10}$ [µg/m³]	-2,21 (-4,71 to 0,28)			
	PM_{10} [µg/m³]	1,62 (-1,31 to 4,55)			
	$FP_{03\text{-}1}$ [#/cm³]	**2,6 (0,4 to 4,9)***	**2,5 (0,01 to 4,9)***	3,9 (-3,6 to 11,3)	3,1 (-0,6 to 6,8)
	$FP_{1\text{-}2.5}$ [#/cm³]	-0,5 (-3,1 to 2,1)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,42 (-2,95 to 2,1)			
SDNN [ms]	UFPs [#/cm³]	1,94 (-3,74 to 7,62)			
	PM_1 [µg/m³]	-4,58 (-9,77 to 0,6)			
	$PM_{2,5}$ [µg/m³]	-4,46 (-9,64 to 0,73)			
	$PM_{2,5\text{-}10}$ [µg/m³]	1,26 (-4,14 to 6,66)			
	PM_{10} [µg/m³]	-4,11 (-9,88 to 1,66)			
	$FP_{03\text{-}1}$ [#/cm³]	**-4,4 (-9,2 to 0,3)°**	**-5,2 (-10,2 to -0,1)***	4,6 (-10,7 to 20)	-3,6 (-11,4 to 4,2)
	$FP_{1\text{-}2.5}$ [#/cm³]	-0,6 (-6 to 4,7)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,89 (-6,03 to 4,24)			
rMSSD [ms]	UFPs [#/cm³]	-3,46 (-16,16 to 11,15)			
	PM_1 [µg/m³]	-2,02 (-14,13 to 11,79)			
	$PM_{2,5}$ [µg/m³]	-1,57 (-13,67 to 12,23)			
	$PM_{2,5\text{-}10}$ [µg/m³]	3,89 (-7,88 to 17,18)			
	PM_{10} [µg/m³]	-0,86 (-13,96 to 14,24)			
	$FP_{03\text{-}1}$ [#/cm³]	-1,9 (-14,2 to 10,6)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-2,4 (-15,3 to 10,6)			
	$CP_{2,5\text{-}10}$ [#/cm³]	5,38 (-6,25 to 18,46)			
PNN50 [%]	UFPs [#/cm³]	-3,9 (-33,8 to 39,51)			
	PM_1 [µg/m³]	-4,94 (-33,31 to 35,5)			
	$PM_{2,5}$ [µg/m³]	-4,27 (-32,66 to 36,1)			
	$PM_{2,5\text{-}10}$ [µg/m³]	3,89 (-24,78 to 43,5)			
	PM_{10} [µg/m³]	-3,68 (-34,04 to 40,67)			
	$FP_{03\text{-}1}$ [#/cm³]	-2,6 (-35,4 to 31,4)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-17,6 (-51,5 to 17,4)			
	$CP_{2,5\text{-}10}$ [#/cm³]	25,65 (-6,88 to 69,53)			

SDANN [ms]	UFPs [#/cm³]	2,83 (-3,36 to 9,02)			
	PM_1 [μg/m³]	-4,13 (-10,04 to 1,78)			
	$PM_{2,5}$ [μg/m³]	-3,92 (-9,82 to 1,98)			
	$PM_{2,5\text{-}10}$ [μg/m³]	2,22 (-3,59 to 8,03)			
	PM_{10} [μg/m³]	-3,32 (-9,82 to 3,17)			
	$FP_{03\text{-}1}$ [#/cm³]	-4,8 (-10,1 to 0,5)			
	$FP_{1\text{-}2.5}$ [#/cm³]	1,4 (-4,5 to 7,3)			
	$CP_{2,5\text{-}10}$ [#/cm³]	0,3 (-5,27 to 5,87)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

TABLE 8-IV PERCENT CHANGES IN 24-HOUR FREQUENCY DOMAIN HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN 24-HOUR PARTICLES EXPOSURE IN SUBJECTS WITH HIGH HSCRP LEVELS (HSCRP > 1,95 MG/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
TP [ms²]	UFPs [#/cm³]	-3,27 (-15,21 to 10,36)			
	PM_1 [μg/m³]	-0,83 (-10,37 to 9,72)			
	$PM_{2,5}$ [μg/m³]	-0,54 (-10,09 to 10,03)			
	$PM_{2,5\text{-}10}$ [μg/m³]	1,08 (-8,45 to 11,61)			
	PM_{10} [μg/m³]	-0,32 (-10,63 to 11,19)			
	$FP_{03\text{-}1}$ [#/cm³]	2,5 (-7,1 to 12,3)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-1,9 (-11,9 to 8,1)			
	$CP_{2,5\text{-}10}$ [#/cm³]	6,09 (-3,36 to 16,45)			
LF/HF	UFPs [#/cm³]	**29,02 (8,06 to 49,98)***	**47,65 (24,89 to 70,42)***	11,43 (-17,87 to 40,73)	-29,79 (-72,56 to 12,98)
	PM_1 [μg/m³]	0,19 (-4,18 to 4,56)			
	$PM_{2,5}$ [μg/m³]	15,48 (-3,6 to 34,55)			
	$PM_{2,5\text{-}10}$ [μg/m³]	2,68 (-15,23 to 20,6)			
	PM_{10} [μg/m³]	15,55 (-4,92 to 36,02)			
	$FP_{03\text{-}1}$ [#/cm³]	**21,89 (4,02 to 39,76)***	**31,65 (13,17 to 50,13)***	-6,63 (-40,96 to 27,7)	3,71 (-23,99 to 31,4)
	$FP_{1\text{-}2.5}$ [#/cm³]	-0,9 (-5,1 to 3,3)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,71 (-17,38 to 15,95)			
HF [ms²]	UFPs [#/cm³]	-17,58 (-40,64 to 14,46)			
	PM_1 [μg/m³]	5,21 (-19,25 to 37,06)			
	$PM_{2,5}$ [μg/m³]	6,79 (-17,81 to 38,76)			
	$PM_{2,5\text{-}10}$ [μg/m³]	9,95 (-13,86 to 40,33)			
	PM_{10} [μg/m³]	8,98 (-17,61 to 44,16)			
	$FP_{03\text{-}1}$ [#/cm³]	8,2 (-16,9 to 33,9)			
	$FP_{1\text{-}2.5}$ [#/cm³]	5,9 (-19,6 to 32,2)			

	$CP_{2,5-10}$ [#/cm^3]	22,29 (-2,11 to 52,79)			
HF [n.u.]	UFPs [#/cm^3]	-10,65 (-23,78 to 4,73)			
	PM_1 [µg/m^3]	-1,31 (-13,93 to 13,15)			
	$PM_{2,5}$ [µg/m^3]	-0,65 (-13,27 to 13,81)			
	$PM_{2,5-10}$ [µg/m^3]	1,63 (-10,35 to 15,22)			
	PM_{10} [µg/m^3]	-0,32 (-13,83 to 15,3)			
	FP_{03-1} [#/cm^3]	-2,5 (-15,6 to 10,7)			
	$FP_{1-2.5}$ [#/cm^3]	1,8 (-11,4 to 15,1)			
	$CP_{2,5-10}$ [#/cm^3]	6,18 (-5,51 to 19,31)			
LF [ms^2]	UFPs [#/cm^3]	-3,44 (-23,35 to 21,65)			
	PM_1 [µg/m^3]	6,62 (-11,59 to 28,59)			
	$PM_{2,5}$ [µg/m^3]	7,24 (-10,93 to 29,12)			
	$PM_{2,5-10}$ [µg/m^3]	4,65 (-12,61 to 25,31)			
	PM_{10} [µg/m^3]	8,35 (-11,23 to 32,24)			
	FP_{03-1} [#/cm^3]	11,8 (-4,5 to 28,3)			
	$FP_{1-2.5}$ [#/cm^3]	0,3 (-17,5 to 18,5)			
	$CP_{2,5-10}$ [#/cm^3]	11,42 (-5,31 to 31,11)			
LF [n.u.]	UFPs [#/cm^3]	2,49 (-4,92 to 10,47)			
	PM_1 [µg/m^3]	0,07 (-5,8 to 6,3)			
	$PM_{2,5}$ [µg/m^3]	-0,08 (-5,92 to 6,12)			
	$PM_{2,5-10}$ [µg/m^3]	-1,33 (-6,85 to 4,52)			
	PM_{10} [µg/m^3]	-0,36 (-6,62 to 6,33)			
	FP_{03-1} [#/cm^3]	0,7 (-5,3 to 6,6)			
	$FP_{1-2.5}$ [#/cm^3]	-1,9 (-7,7 to 4)			
	$CP_{2,5-10}$ [#/cm^3]	-1,21 (-6,78 to 4,69)			
VLF	UFPs [#/cm^3]	-2,53 (-10,49 to 5,43)			
	PM_1 [µg/m^3]	-3,01 (-9,05 to 3,03)			
	$PM_{2,5}$ [µg/m^3]	-2,8 (-8,86 to 3,27)			
	$PM_{2,5-10}$ [µg/m^3]	2,35 (-3,64 to 8,34)			
	PM_{10} [µg/m^3]	-2,32 (-8,96 to 4,32)			
	FP_{03-1} [#/cm^3]	0,4 (-5,8 to 6,5)			
	$FP_{1-2.5}$ [#/cm^3]	-0,9 (-7,1 to 5,3)			
	$CP_{2,5-10}$ [#/cm^3]	1,41 (-4,68 to 7,51)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

Table 8-V Percent changes in 24-hour time domain HRV indices associated with an interquartile range increase in 24-hour particles exposure in subjects with low hsCRP levels (hsCRP < 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	35	12	16	7
HR [bpm]	UFPs [#/cm³]	-0,52 (-3,32 to 2,29)			
	PM_1 [μg/m³]	-1,1 (-3,84 to 1,64)			
	$PM_{2,5}$ [μg/m³]	-1,08 (-3,74 to 1,58)			
	$PM_{2,5-10}$ [μg/m³]	0,92 (-1,42 to 3,26)			
	PM_{10} [μg/m³]	-0,78 (-3,5 to 1,94)			
	FP_{03-1} [#/cm³]	-0,6 (-2,7 to 1,6)			
	$FP_{1-2.5}$ [#/cm³]	-0,5 (-2,9 to 2)			
	$CP_{2,5-10}$ [#/cm³]	-0,54 (-2,54 to 1,47)			
SDNN [ms]	UFPs [#/cm³]	2,92 (-5,61 to 11,45)			
	PM_1 [μg/m³]	7,3 (-0,82 to 15,41)			
	$PM_{2,5}$ [μg/m³]	6,55 (-1,35 to 14,46)			
	$PM_{2,5-10}$ [μg/m³]	-3,51 (-10,64 to 3,63)			
	PM_{10} [μg/m³]	5,03 (-3,12 to 13,18)			
	FP_{03-1} [#/cm³]	3,2 (-3,3 to 9,8)			
	$FP_{1-2.5}$ [#/cm³]	-0,1 (-7,5 to 7,4)			
	$CP_{2,5-10}$ [#/cm³]	-2,93 (-8,95 to 3,09)			
rMSSD [ms]	UFPs [#/cm³]	9,91 (-3,92 to 25,72)			
	PM_1 [μg/m³]	9,64 (-3,69 to 24,82)			
	$PM_{2,5}$ [μg/m³]	9,4 (-3,48 to 24)			
	$PM_{2,5-10}$ [μg/m³]	-1,42 (-12,26 to 10,75)			
	PM_{10} [μg/m³]	7,93 (-5,09 to 22,73)			
	FP_{03-1} [#/cm³]	3,1 (-7,6 to 13,8)			
	$FP_{1-2.5}$ [#/cm³]	2,4 (-9,5 to 14,4)			
	$CP_{2,5-10}$ [#/cm³]	3,3 (-6,57 to 14,21)			
PNN50 [%]	UFPs [#/cm³]	10,1 (-23,76 to 58,98)			
	PM_1 [μg/m³]	22,12 (-14,24 to 73,9)			
	$PM_{2,5}$ [μg/m³]	21,51 (-13,7 to 71,09)			
	$PM_{2,5-10}$ [μg/m³]	-3,78 (-29,58 to 31,46)			
	PM_{10} [μg/m³]	17,85 (-16,96 to 67,26)			
	FP_{03-1} [#/cm³]	4,7 (-23,8 to 34)			
	$FP_{1-2.5}$ [#/cm³]	6,1 (-25,6 to 38,9)			
	$CP_{2,5-10}$ [#/cm³]	7,46 (-17,88 to 40,61)			

SDANN [ms]	UFPs [#/cm^3]	3,05 (-6,81 to 12,91)			
	PM_1 [µg/m^3]	8,39 (-0,94 to 17,71)			
	$PM_{2,5}$ [µg/m^3]	7,53 (-1,57 to 16,63)			
	$PM_{2,5-10}$ [µg/m^3]	-2,97 (-11,19 to 5,26)			
	PM_{10} [µg/m^3]	6,06 (-3,33 to 15,45)			
	FP_{03-1} [#/cm^3]	4,9 (-2,5 to 12,3)			
	$FP_{1-2.5}$ [#/cm^3]	0,7 (-7,8 to 9,2)			
	$CP_{2,5-10}$ [#/cm^3]	-2,19 (-9,07 to 4,69)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

TABLE 8-VI PERCENT CHANGES IN 24-HOUR FREQUENCY DOMAIN HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN 24-HOUR PARTICLES EXPOSURE IN SUBJECTS WITH LOW HSCRP LEVELS (HSCRP < 1,95 MG/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	35	12	16	7
TP [ms^2]	UFPs [#/cm^3]	5,09 (-11,27 to 24,46)			
	PM_1 [µg/m^3]	6,9 (-9,25 to 25,92)			
	$PM_{2,5}$ [µg/m^3]	6,35 (-9,26 to 24,64)			
	$PM_{2,5-10}$ [µg/m^3]	-7,76 (-19,96 to 6,3)			
	PM_{10} [µg/m^3]	3,7 (-11,82 to 21,96)			
	FP_{03-1} [#/cm^3]	-1,8 (-14,9 to 11,4)			
	$FP_{1-2.5}$ [#/cm^3]	-5,5 (-20,1 to 9,4)			
	$CP_{2,5-10}$ [#/cm^3]	-4,23 (-15,33 to 8,31)			
LF/HF	UFPs [#/cm^3]	-7,37 (-17,31 to 2,57)			
	PM_1 [µg/m^3]	-1,56 (-3,76 to 0,65)			
	$PM_{2,5}$ [µg/m^3]	**-10,64 (-19,39 to -1,9)***	**-22,56 (-34,95 to -10,17)***	-2,3 (-13,19 to 8,58)	-10,78 (-25,31 to 3,76)
	$PM_{2,5-10}$ [µg/m^3]	-6,52 (-14,96 to 1,92)			
	PM_{10} [µg/m^3]	**-10,8 (-19,68 to -1,92)***	**-25,09 (-38,93 to -11,26)***	-1,88 (-13 to 9,25)	-11,82 (-27,07 to 3,44)
	FP_{03-1} [#/cm^3]	**-9,8 (-17,05 to -2,55)***	**-20,24 (-30,64 to -9,85)***	-4,22 (-13,85 to 5,41)	-6,26 (-18,27 to 5,75)
	$FP_{1-2.5}$ [#/cm^3]	-1,6 (-3,6 to 0,4)			
	$CP_{2,5-10}$ [#/cm^3]	-5,73 (-13,24 to 1,77)			
HF [ms^2]	UFPs [#/cm^3]	14,46 (-9,94 to 45,46)			
	PM_1 [µg/m^3]	13,43 (-10,21 to 43,31)			
	$PM_{2,5}$ [µg/m^3]	13,31 (-9,58 to 41,99)			
	$PM_{2,5-10}$ [µg/m^3]	-5,13 (-23,13 to 17,09)			
	PM_{10} [µg/m^3]	10,38 (-12,39 to 39,07)			
	FP_{03-1} [#/cm^3]	2,6 (-16,7 to 22,3)			

	$FP_{1\text{-}2.5}$ [#/cm^{3}]	4,1 (-17,3 to 25,9)			
	$CP_{2,5\text{-}10}$ [#/cm^{3}]	1,03 (-16,01 to 21,54)			
HF [n.u.]	UFPs [#/cm^{3}]	5,91 (-1,14 to 13,46)			
	PM_{1} [μg/m^{3}]	**7,02 (0,4 to 14,08)***	**11,38 (1,32 to 22,45)***	5,86 (-3,21 to 15,78)	2,79 (-8,86 to 15,93)
	$PM_{2,5}$ [μg/m^{3}]	**6,95 (0,59 to 13,72)***	**11,74 (1,6 to 22,88)***	6,01 (-2,72 to 15,51)	2,84 (-8,03 to 14,99)
	$PM_{2,5\text{-}10}$ [μg/m^{3}]	3,81 (-2,26 to 10,25)			
	PM_{10} [μg/m^{3}]	**6,95 (0,5 to 13,81)***	**13,04 (1,68 to 25,66)***	5,36 (-3,47 to 15,01)	3,06 (-8,32 to 15,85)
	$FP_{03\text{-}1}$ [#/cm^{3}]	**5,7 (0,4 to 11,1)***	**9,4 (1,2 to 17,7)***	5,2 (-2,6 to 13,1)	2 (-7,4 to 11,5)
	$FP_{1\text{-}2.5}$ [#/cm^{3}]	**5,6 (-0,4 to 11,6)°**	**9,6 (-0,6 to 19,9)°**	5 (-3,1 to 13,2)	0,7 (-10,9 to 12,4)
	$CP_{2,5\text{-}10}$ [#/cm^{3}]	3,67 (-1,76 to 9,41)			
LF [ms^{2}]	UFPs [#/cm^{3}]	6,17 (-12,53 to 28,87)			
	PM_{1} [μg/m^{3}]	6,58 (-11,84 to 28,85)			
	$PM_{2,5}$ [μg/m^{3}]	5,94 (-11,85 to 27,32)			
	$PM_{2,5\text{-}10}$ [μg/m^{3}]	-10,6 (-24,18 to 5,4)			
	PM_{10} [μg/m^{3}]	2,65 (-14,94 to 23,88)			
	$FP_{03\text{-}1}$ [#/cm^{3}]	-1,9 (-17,2 to 13,6)			
	$FP_{1\text{-}2.5}$ [#/cm^{3}]	-3,2 (-20,3 to 14,2)			
	$CP_{2,5\text{-}10}$ [#/cm^{3}]	-5,42 (-18,21 to 9,36)			
LF [n.u.]	UFPs [#/cm^{3}]	-2,07 (-6,3 to 2,36)			
	PM_{1} [μg/m^{3}]	-0,53 (-4,78 to 3,91)			
	$PM_{2,5}$ [μg/m^{3}]	-0,82 (-4,93 to 3,47)			
	$PM_{2,5\text{-}10}$ [μg/m^{3}]	-2,61 (-6,17 to 1,08)			
	PM_{10} [μg/m^{3}]	-1,29 (-5,43 to 3,03)			
	$FP_{03\text{-}1}$ [#/cm^{3}]	0,1 (-3,4 to 3,7)			
	$FP_{1\text{-}2.5}$ [#/cm^{3}]	-1,2 (-5,1 to 2,7)			
	$CP_{2,5\text{-}10}$ [#/cm^{3}]	-2,02 (-5,24 to 1,32)			
VLF	UFPs [#/cm^{3}]	0,94 (-15,67 to 17,55)			
	PM_{1} [μg/m^{3}]	5,87 (-10,2 to 21,95)			
	$PM_{2,5}$ [μg/m^{3}]	5,41 (-10,2 to 21,02)			
	$PM_{2,5\text{-}10}$ [μg/m^{3}]	-8,31 (-22 to 5,38)			
	PM_{10} [μg/m^{3}]	2,87 (-13,1 to 18,84)			
	$FP_{03\text{-}1}$ [#/cm^{3}]	0,6 (-12 to 13,3)			
	$FP_{1\text{-}2.5}$ [#/cm^{3}]	-6,3 (-20,5 to 7,9)			
	$CP_{2,5\text{-}10}$ [#/cm^{3}]	-4,7 (-16,25 to 6,84)			

Notes: *$p < 0,05$; °Borderline statistical significance ($p < 0,07$).

<u>TABLE 8-VII</u> PERCENT CHANGES IN DAY HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE.

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	77	26	34	17
HR [bpm]	UFPs [#/cm³]	-0,03 (-1,82 to 1,75)			
	$FP_{03\text{-}1}$ [#/cm³]	**1,77 (0,35 to 3,19)***	**2,19 (0,27 to 4,1)***	1,42 (-0,97 to 3,81)	1,38 (-1,26 to 4,02)
	$FP_{1\text{-}2.5}$ [#/cm³]	1,09 (-0,45 to 2,62)			
	$CP_{2,5\text{-}10}$ [#/cm³]	0,86 (-0,37 to 2,08)			
SDNN [ms]	UFPs [#/cm³]	-1,34 (-6,23 to 3,55)			
	$FP_{03\text{-}1}$ [#/cm³]	-1,93 (-5,93 to 2,08)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-2,76 (-7,02 to 1,5)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,14 (-3,54 to 3,26)			
rMSSD [ms]	UFPs [#/cm³]	3,21 (-5,73 to 12,99)			
	$FP_{03\text{-}1}$ [#/cm³]	-3,03 (-10,06 to 4,56)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-1 (-8,56 to 7,19)			
	$CP_{2,5\text{-}10}$ [#/cm³]	4,7 (-1,68 to 11,49)			
PNN50 [%]	UFPs [#/cm³]	12,47 (-12,7 to 44,88)			
	$FP_{03\text{-}1}$ [#/cm³]	-8,74 (-26,18 to 12,81)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-10,76 (-28,64 to 11,59)			
	$CP_{2,5\text{-}10}$ [#/cm³]	12,01 (-6,06 to 33,55)			
SDANN [ms]	UFPs [#/cm³]	-1,21 (-7,07 to 4,66)			
	$FP_{03\text{-}1}$ [#/cm³]	0,16 (-4,75 to 5,07)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-1,86 (-7,09 to 3,36)			
	$CP_{2,5\text{-}10}$ [#/cm³]	0,23 (-3,84 to 4,29)			
TP [ms²]	UFPs [#/cm³]	-0,36 (-9,69 to 9,94)			
	$FP_{03\text{-}1}$ [#/cm³]	-6,81 (-13,98 to 0,97)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-6,17 (-13,76 to 2,09)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-1,29 (-7,81 to 5,7)			
LF/HF	UFPs [#/cm³]	1,75 (-6,18 to 9,68)			
	$FP_{03\text{-}1}$ [#/cm³]	3,94 (-2,52 to 10,41)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-0,48 (-2,52 to 1,56)			
	$CP_{2,5\text{-}10}$ [#/cm³]	-4,13 (-9,65 to 1,39)			
HF [ms²]	UFPs [#/cm³]	7,47 (-9,35 to 27,41)			
	$FP_{03\text{-}1}$ [#/cm³]	-4,5 (-17,16 to 10,1)			
	$FP_{1\text{-}2.5}$ [#/cm³]	-2,41 (-15,96 to 13,33)			
	$CP_{2,5\text{-}10}$ [#/cm³]	5,49 (-6,42 to 18,91)			
HF n.u.	UFPs [#/cm³]	3,84 (-3,32 to 11,53)			
	$FP_{03\text{-}1}$ [#/cm³]	0,48 (-5,37 to 6,69)			
	$FP_{1\text{-}2.5}$ [#/cm³]	0,87 (-5,31 to 7,45)			

	$CP_{2,5-10}$ [#/cm^3]	4,54 (-0,53 to 9,86)			
LF [ms^2]	UFPs [#/cm^3]	1,49 (-11,09 to 15,85)			
	FP_{03-1} [#/cm^3]	-4,72 (-14,65 to 6,37)			
	$FP_{1-2.5}$ [#/cm^3]	-4,48 (-14,94 to 7,26)			
	$CP_{2,5-10}$ [#/cm^3]	-2,15 (-10,74 to 7,26)			
LF n.u.	UFPs [#/cm^3]	-1,32 (-5,79 to 3,36)			
	FP_{03-1} [#/cm^3]	0,75 (-3,05 to 4,7)			
	$FP_{1-2.5}$ [#/cm^3]	-1,29 (-5,18 to 2,76)			
	$CP_{2,5-10}$ [#/cm^3]	**-3,74 (-6,69 to -0,7)***	-4,08 (-8,69 to 0,77)	-3,48 (-8,21 to 1,49)	-3,58 (-9,71 to 2,97)
VLF [ms^2]	UFPs [#/cm^3]	-3,48 (-15,25 to 8,28)			
	FP_{03-1} [#/cm^3]	**-12,33 (-21,92 to -2,74)***	**-13,56 (-26,6 to -0,53)***	-11,92 (-27,6 to 3,76)	-10,18 (-28,57 to 8,21)
	$FP_{1-2.5}$ [#/cm^3]	**-13,06 (-23,35 to -2,77)***	-12,53 (-27,6 to 2,54)	-13,69 (-29,46 to 2,07)	-12,95 (-32,29 to 6,39)
	$CP_{2,5-10}$ [#/cm^3]	-5,55 (-13,6 to 2,5)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

<u>TABLE 8-VIII</u> PERCENT CHANGES IN DAY HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE IN SUBJECTS WITH HIGH HSCRP LEVELS (HSCRP > 1,95 MG/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
HR [bpm]	UFPs [#/cm^3]	-0,45 (-3,01 to 2,1)			
	FP_{03-1} [#/cm^3]	1,27 (-1,08 to 3,62)			
	$FP_{1-2.5}$ [#/cm^3]	0,2 (-2,09 to 2,49)			
	$CP_{2,5-10}$ [#/cm^3]	0,92 (-0,97 to 2,81)			
SDNN [ms]	UFPs [#/cm^3]	-3,27 (-9,74 to 3,2)			
	FP_{03-1} [#/cm^3]	-2,72 (-8,89 to 3,45)			
	$FP_{1-2.5}$ [#/cm^3]	-4,52 (-10,17 to 1,13)			
	$CP_{2,5-10}$ [#/cm^3]	-0,38 (-5,26 to 4,49)			
rMSSD [ms]	UFPs [#/cm^3]	-1,86 (-14,44 to 12,57)			
	FP_{03-1} [#/cm^3]	2,72 (-9,76 to 16,93)			
	$FP_{1-2.5}$ [#/cm^3]	1,09 (-10,85 to 14,63)			
	$CP_{2,5-10}$ [#/cm^3]	**13,4 (3,25 to 24,54)***	**22,72 (6,7 to 41,15)***	11,9 (-7,15 to 34,87)	4,08 (-11,88 to 22,93)
PNN50 [%]	UFPs [#/cm^3]	3,58 (-26,9 to 46,78)			
	FP_{03-1} [#/cm^3]	17,3 (-15,25 to 62,34)			
	$FP_{1-2.5}$ [#/cm^3]	-8,28 (-33,58 to 26,66)			
	$CP_{2,5-10}$ [#/cm^3]	**37,18 (7,86 to 74,47)***	**53,42 (5,46 to 123,17)***	31,41 (-19,3 to 114)	22,64 (-21,71 to 92,13)
AN N	UFPs [#/cm^3]	-4,46 (-12,34 to 3,43)			
	FP_{03-1} [#/cm^3]	-2,46 (-10,35 to 5,43)			

	FP$_{1-2.5}$ [#/cm^3]	-4,46 (-11,9 to 2,97)			
	CP$_{2,5-10}$ [#/cm^3]	-0,69 (-6,6 to 5,22)			
TP [ms^2]	UFPs [#/cm^3]	0,21 (-10,05 to 11,63)			
	FP$_{03-1}$ [#/cm^3]	-0,96 (-10,02 to 9,02)			
	FP$_{1-2.5}$ [#/cm^3]	-4,85 (-13,16 to 4,26)			
	CP$_{2,5-10}$ [#/cm^3]	2,18 (-5,83 to 10,87)			
LF/HF	UFPs [#/cm^3]	8,67 (-4,17 to 21,51)			
	FP$_{03-1}$ [#/cm^3]	2,18 (-10,12 to 14,48)			
	FP$_{1-2.5}$ [#/cm^3]	-1,4 (-5,17 to 2,36)			
	CP$_{2,5-10}$ [#/cm^3]	**-10,66 (-19,8 to -1,53)***	**-15,94 (-29,95 to -1,93)***	-2,88 (-21,8 to 16,03)	-11,19 (-27,8 to 5,42)
HF [ms^2]	UFPs [#/cm^3]	3,46 (-20,71 to 35)			
	FP$_{03-1}$ [#/cm^3]	16,13 (-8,86 to 47,97)			
	FP$_{1-2.5}$ [#/cm^3]	5,93 (-16,85 to 34,96)			
	CP$_{2,5-10}$ [#/cm^3]	**27,74 (6,29 to 53,51)***	**39,4 (5,1 to 84,89)***	31,34 (-10,01 to 91,69)	10,3 (-21,15 to 54,3)
HF n.u.	UFPs [#/cm^3]	1,47 (-10,18 to 14,63)			
	FP$_{03-1}$ [#/cm^3]	8,66 (-2,81 to 21,49)			
	FP$_{1-2.5}$ [#/cm^3]	3,43 (-7,47 to 15,63)			
	CP$_{2,5-10}$ [#/cm^3]	**13,34 (4,51 to 22,91)***	**17,32 (3,46 to 33,05)***	11,75 (-5,54 to 32,22)	9,7 (-5,53 to 27,4)
LF [ms^2]	UFPs [#/cm^3]	6,42 (-10,49 to 26,52)			
	FP$_{03-1}$ [#/cm^3]	9,08 (-6,76 to 27,61)			
	FP$_{1-2.5}$ [#/cm^3]	-0,89 (-15,39 to 16,1)			
	CP$_{2,5-10}$ [#/cm^3]	5,11 (-8,03 to 20,12)			
LF n.u.	UFPs [#/cm^3]	1,53 (-6,59 to 10,36)			
	FP$_{03-1}$ [#/cm^3]	1,06 (-6,55 to 9,3)			
	FP$_{1-2.5}$ [#/cm^3]	-2,94 (-9,93 to 4,59)			
	CP$_{2,5-10}$ [#/cm^3]	**-7,13 (-12,17 to -1,8)***	**-10,23 (-17,7 to -2,09)***	-0,04 (-11,18 to 12,51)	-8,77 (-17,68 to 1,1)
VLF [ms^2]	UFPs [#/cm^3]	-1,73 (-10,83 to 7,36)			
	FP$_{03-1}$ [#/cm^3]	-6,8 (-14,41 to 0,81)			
	FP$_{1-2.5}$ [#/cm^3]	**-8,42 (-15,37 to -1,46)***	-6,1 (-14,13 to 1,93)	-14,56 (-33,89 to 4,77)	**-12,96 (-26,01 to 0,08)°**
	CP$_{2,5-10}$ [#/cm^3]	-5,05 (-11,69 to 1,59)			

Notes: *$p < 0,05$; °Borderline statistical significance ($p < 0,07$).

TABLE 8-IX PERCENT CHANGES IN DAY HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE **IN** SUBJECTS WITH LOW HSCRP LEVELS (HSCRP < 1,95 MG/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	37	13	17	7
HR [bpm]	UFPs [#/cm³]	-0,05 (-3,02 to 2,92)			
	FP_{03-1} [#/cm³]	0,93 (-1,69 to 3,56)			
	$FP_{1-2.5}$ [#/cm³]	0,76 (-1,97 to 3,49)			
	$CP_{2,5-10}$ [#/cm³]	-0,05 (-2,24 to 2,14)			
SDNN [ms]	UFPs [#/cm³]	4,46 (-4,32 to 13,25)			
	FP_{03-1} [#/cm³]	2,07 (-5,67 to 9,82)			
	$FP_{1-2.5}$ [#/cm³]	-1,46 (-9,58 to 6,66)			
	$CP_{2,5-10}$ [#/cm³]	-0,99 (-7,41 to 5,43)			
rMSSD [ms]	UFPs [#/cm³]	9,35 (-3,89 to 24,42)			
	FP_{03-1} [#/cm³]	-1,94 (-12,7 to 10,16)			
	$FP_{1-2.5}$ [#/cm³]	1,21 (-9,96 to 13,76)			
	$CP_{2,5-10}$ [#/cm³]	1,58 (-7,67 to 11,75)			
PNN50 [%]	UFPs [#/cm³]	7,83 (-23,63 to 52,26)			
	FP_{03-1} [#/cm³]	-9,71 (-33,65 to 22,86)			
	$FP_{1-2.5}$ [#/cm³]	-1,07 (-27,42 to 34,85)			
	$CP_{2,5-10}$ [#/cm³]	1,4 (-21,43 to 30,88)			
SDANN [ms]	UFPs [#/cm³]	5,74 (-4,53 to 16,01)			
	FP_{03-1} [#/cm³]	4,76 (-4,22 to 13,75)			
	$FP_{1-2.5}$ [#/cm³]	-1,23 (-10,78 to 8,31)			
	$CP_{2,5-10}$ [#/cm³]	-0,56 (-8,04 to 6,92)			
TP [ms²]	UFPs [#/cm³]	8,6 (-7,88 to 28,04)			
	FP_{03-1} [#/cm³]	-6,59 (-19,03 to 7,77)			
	$FP_{1-2.5}$ [#/cm³]	-5,4 (-18,57 to 9,91)			
	$CP_{2,5-10}$ [#/cm³]	-3,91 (-14,74 to 8,29)			
LF/HF	UFPs [#/cm³]	-3,35 (-12,9 to 6,19)			
	FP_{03-1} [#/cm³]	0,07 (-8,64 to 8,78)			
	$FP_{1-2.5}$ [#/cm³]	-0,18 (-2,38 to 2,02)			
	$CP_{2,5-10}$ [#/cm³]	-3,23 (-10,37 to 3,91)			
HF [ms²]	UFPs [#/cm³]	9,79 (-13,11 to 38,73)			
	FP_{03-1} [#/cm³]	-10,51 (-27,65 to 10,69)			
	$FP_{1-2.5}$ [#/cm³]	-3,99 (-22,3 to 18,64)			
	$CP_{2,5-10}$ [#/cm³]	-2,85 (-18,54 to 15,85)			
HF n.u.	UFPs [#/cm³]	2,83 (-4,55 to 10,79)			
	FP_{03-1} [#/cm³]	-0,84 (-7,45 to 6,25)			
	$FP_{1-2.5}$ [#/cm³]	-0,75 (-7,07 to 6,01)			

	$CP_{2,5-10}$ [#/cm^3]	2,42 (-3,09 to 8,23)			
LF [ms^2]	UFPs [#/cm^3]	2,86 (-13,52 to 22,34)			
	FP_{03-1} [#/cm^3]	-10,15 (-22,97 to 4,8)			
	$FP_{1-2.5}$ [#/cm^3]	-5,9 (-19,76 to 10,35)			
	$CP_{2,5-10}$ [#/cm^3]	-8,13 (-19,18 to 4,43)			
LF n.u.	UFPs [#/cm^3]	-3,73 (-8,23 to 0,98)			
	FP_{03-1} [#/cm^3]	-1,15 (-5,45 to 3,35)			
	$FP_{1-2.5}$ [#/cm^3]	-1,51 (-5,69 to 2,86)			
	$CP_{2,5-10}$ [#/cm^3]	-2,85 (-6,18 to 0,6)			
VLF [ms^2]	UFPs [#/cm^3]	4,79 (-12,18 to 21,76)			
	FP_{03-1} [#/cm^3]	-2,17 (-16,88 to 12,55)			
	$FP_{1-2.5}$ [#/cm^3]	-4,61 (-20,28 to 11,05)			
	$CP_{2,5-10}$ [#/cm^3]	-4,52 (-16,71 to 7,67)			

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

TABLE 8-X PERCENT CHANGES IN NIGHT-TIME HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN NIGHT-TIME PARTICLES EXPOSURE.

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	79	27	34	18
HR [bpm]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	0,68 (-0,95 to 2,3)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-0,45 (-1,62 to 0,72)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	0,41 (-1,11 to 1,92)	-	-	-
SDNN [ms]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	**-5,69 (-10,76 to - 0,62)***	-4,28 (-10,52 to 1,96)	**-8,61 (-17,57 to 0,35)°**	-6,3 (-15,82 to 3,22)
	$FP_{1-2.5}$ [#/cm^3]	-1,05 (-4,79 to 2,69)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	0,9 (-3,94 to 5,74)	-	-	-
rMSSD [ms]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	-0,56 (-9,46 to 9,21)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-1 (-7,44 to 5,87)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	7,87 (-1,08 to 17,63)	-	-	-
PNN50 [%]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	-4,77 (-25,46 to 21,66)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-3,44 (-18,94 to 15,03)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	14,41 (-8,87 to 43,65)	-	-	-
SDANN [ms]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	**-6,6 (-13,18 to -0,02)***	-5,06 (-13,34 to 3,21)	-8,78 (-20 to 2,44)	-8,17 (-21,46 to 5,11)
	$FP_{1-2.5}$ [#/cm^3]	-0,75 (-5,51 to 4)	-	-	-

	CP$_{2,5-10}$ [#/cm^3]	-2,28 (-8,46 to 3,89)	-	-	-
TP [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	-2,85 (-12,82 to 8,26)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	-3,46 (-10,68 to 4,34)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	4,85 (-5,16 to 15,93)	-	-	-
LF/HF	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	6,58 (-5,24 to 18,41)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	-0,84 (-3,03 to 1,36)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	-2,85 (-13,88 to 8,17)	-	-	-
HF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	-2,67 (-19,27 to 17,34)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	0,28 (-12,31 to 14,69)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	13,37 (-4,64 to 34,79)	-	-	-
HF n.u.	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	-3,12 (-11,02 to 5,48)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	1,92 (-4,09 to 8,3)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	2,86 (-4,99 to 11,36)	-	-	-
LF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	0,78 (-11,63 to 14,92)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	-2,05 (-10,87 to 7,64)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	5,76 (-6,37 to 19,46)	-	-	-
LF n.u.	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	0,33 (-4,16 to 5,03)	-	-	-
	FP$_{1-2.5}$ [#/cm^3]	-1,51 (-4,67 to 1,75)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	**-5,76 (-9,61 to -1,75)***	-1,57 (-8,43 to 5,81)	**-8,85 (-14,32 to -3,04)***	-5,45 (-13,2 to 3)
VLF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP$_{03-1}$ [#/cm^3]	**-18,77 (-35,55--2)***	-14,75 (-35,79-6,29)	**-30,7 (-59,09--2,31)***	-13 (-46,95-20,95)
	FP$_{1-2.5}$ [#/cm^3]	-9,26 (-21,26 to 2,73)	-	-	-
	CP$_{2,5-10}$ [#/cm^3]	-4,37 (-20,11 to 11,38)	-	-	-

Notes: [a] Insufficient UFPs night-time data for analysis; *p < 0,05; °Borderline statistical significance (p < 0,07).

Table 8-XI Percent changes in night-time HRV indices associated with an interquartile range increase in night-time particles exposure in subjects with high hsCRP levels (hsCRP > 1,95 mg/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
HR [bpm]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	0,85 (-1,7 to 3,39)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-1,83 (-3,96 to 0,29)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	0,91 (-1,35 to 3,16)	-	-	-
SDNN [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-5,55 (-12,96 to 1,86)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	1,36 (-5,13 to 7,86)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	0,32 (-6,42 to 7,07)	-	-	-
rMSSD [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-2,96 (-16,47 to 12,74)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	2,85 (-9,62 to 17,05)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	7,95 (-5,43 to 23,22)	-	-	-
PNN50 [%]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-12,63 (-39,76 to 26,73)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	0,08 (-27,4 to 37,97)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	16,21 (-16,36 to 61,47)	-	-	-
SDANN [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	**-11,49 (-22,46 to -0,52)***	-10,03 (-22,19 to 2,14)	-12,07 (-36,24 to 12,1)	-18,31 (-39,46 to 2,83)
	$FP_{1-2.5}$ [#/cm³]	-2,28 (-11,99 to 7,43)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-2,75 (-12,45 to 6,94)	-	-	-
TP [ms²]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	3,71 (-8,63 to 17,73)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	2,92 (-8,05 to 15,19)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	5,52 (-5,97 to 18,42)	-	-	-
LF/HF	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	**22,42 (2,95 to 41,89)***	**33,26 (12,33 to 54,19)***	0,35 (-40,25 to 40,94)	-14,35 (-50,43 to 21,73)
	$FP_{1-2.5}$ [#/cm³]	-3,75 (-8,76 to 1,26)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-9,16 (-26,19 to 7,87)	-	-	-
HF [ms²]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-5,01 (-30,19 to 29,25)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	8,46 (-16,83 to 41,43)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	25,09 (-4,19 to 63,33)	-	-	-
HF n.u.	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-8,99 (-21,56 to 5,59)	-	-	-

	$FP_{1-2.5}$ [#/cm³]	8,15 (-5,1 to 23,25)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	11,25 (-2,27 to 26,64)	-	-	-
LF [ms²]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	12,82 (-3,16 to 31,44)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	1,16 (-12,32 to 16,72)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	9,76 (-4,97 to 26,79)	-	-	-
LF n.u.	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	0,42 (-8,27 to 9,92)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-6,67 (-13,52 to 0,73)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-6,71 (-13,5 to 0,61)	-	-	-
VLF [ms²]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-9,3 (-33,71 to 15,1)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-0,48 (-21,58 to 20,62)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-2,19 (-24,21 to 19,84)	-	-	-

Notes: [a] Insufficient UFPs night-time data for analysis; *p < 0,05; °Borderline statistical significance (p < 0,07).

<u>TABLE 8-XII</u> PERCENT CHANGES IN NIGHT-TIME HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN NIGHT-TIME PARTICLES EXPOSURE IN SUBJECTS WITH LOW HSCRP LEVELS (HSCRP < 1,95 MG/L).

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	39	14	17	8
HR [bpm]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-0,79 (-3,08 to 1,51)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	0,05 (-1,5 to 1,6)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	0,4 (-1,83 to 2,63)	-	-	-
SDNN [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-2,71 (-10,98 to 5,55)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-1,61 (-7,3 to 4,08)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-2,72 (-10,63 to 5,19)	-	-	-
rMSSD [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	6,8 (-6 to 21,34)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	0,35 (-8,36 to 9,88)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	1,74 (-10,06 to 15,1)	-	-	-
PNN50 [%]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	8,72 (-23,35 to 54,2)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-3,71 (-24,3 to 22,47)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	2,79 (-26,8 to 44,35)	-	-	-
SDANN [ms]	UFPs [#/cm³][a]	-	-	-	-
	FP_{03-1} [#/cm³]	-1,61 (-11,33 to 8,1)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-0,53 (-6,95 to 5,89)	-	-	-

	$CP_{2,5-10}$ [#/cm^3]	-2,15 (-11,74 to 7,44)	-	-	-
TP [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	2,16 (-14,23 to 21,7)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-4 (-15,13 to 8,59)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	-1,11 (-16,2 to 16,7)	-	-	-
LF/HF	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	**-20,41 (-35,29 to -5,52)***	**-28,69 (-47,46 to -9,91)***	-8,53 (-32,65 to 15,6)	-12,74 (-44,77 to 19,3)
	$FP_{1-2.5}$ [#/cm^3]	**-3,17 (-5,33 to -1)***	**-3,88 (-6,8--0,96)***	-3,4 (-7,14 to 0,35)	1,34 (-4 to 6,68)
	$CP_{2,5-10}$ [#/cm^3]	-6,09 (-21,4 to 9,22)	-	-	-
HF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	13,1 (-11,73 to 44,91)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	3,82 (-13,24 to 24,23)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	0,54 (-20,66 to 27,4)	-	-	-
HF n.u.	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	**12,21 (2,67 to 22,64)***	**15,43 (3,09 to 29,25)***	11,87 (-3,42 to 29,59)	3,84 (-13,97 to 25,34)
	$FP_{1-2.5}$ [#/cm^3]	**7,09 (0,12 to 14,55)***	**10,05 (0,57 to 20,42)***	7,09 (-4,79 to 20,46)	-5,62 (-19,93 to 11,26)
	$CP_{2,5-10}$ [#/cm^3]	2,19 (-6,85 to 12,09)	-	-	-
LF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	1,24 (-17,87 to 24,79)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-4,99 (-17,98 to 10,04)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	-6,05 (-22,93 to 14,51)	-	-	-
LF n.u.	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	-2,07 (-6,64 to 2,71)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	**-3,63 (-6,75 to -0,41)***	-3,98 (-8,1 to 0,34)	**-5,46 (-10,71 to 0,09)°**	2,42 (-5,48 to 10,98)
	$CP_{2,5-10}$ [#/cm^3]	-3,8 (-7,99 to 0,59)	-	-	-
VLF [ms^2]	UFPs [#/cm^3][a]	-	-	-	-
	FP_{03-1} [#/cm^3]	-0,98 (-15,33 to 13,37)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-5,84 (-15,59 to 3,91)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	-3,91 (-17,6 to 9,77)	-	-	-

Notes: [a] Insufficient UFPs night-time data for analysis; *$p < 0,05$; °Borderline statistical significance ($p < 0,07$).

TABLE 8-XIII PERCENT CHANGES IN NIGHT-TIME HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE.

		Total Group	"Healthy" Group	Heart Group	Lung Group
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	79	27	34	18
HR [bpm]	UFPs [#/cm³]	-0,38 (-2,26 to 1,49)	-	-	-
	FP_{03-1} [#/cm³]	0,8 (-0,75 to 2,34)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-0,89 (-2,39 to 0,61)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	0,3 (-1,01 to 1,61)	-	-	-
SDNN [ms]	UFPs [#/cm³]	-1,36 (-7,44 to 4,72)	-	-	-
	FP_{03-1} [#/cm³]	**-7,88 (-12,67 to -3,1)***	**-6,77 (-13,41 to -0,13)***	**-8,36 (-16,22 to -0,49)***	**-9,08 (-17,18 to -0,98)***
	$FP_{1-2.5}$ [#/cm³]	-3,26 (-8,1 to 1,58)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-2,2 (-6,45 to 2,05)	-	-	-
rMSSD [ms]	UFPs [#/cm³]	-0,86 (-11,04 to 10,48)	-	-	-
	FP_{03-1} [#/cm³]	-2,02 (-10,51 to 7,28)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	1,48 (-6,95 to 10,68)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	5,85 (-1,86 to 14,15)	-	-	-
PNN50 [%]	UFPs [#/cm³]	-9,27 (-31,45 to 20,09)	-	-	-
	FP_{03-1} [#/cm³]	-4,35 (-24,64 to 21,4)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	1,35 (-19,51 to 27,63)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	10,92 (-9,07 to 35,31)	-	-	-
SDANN [ms]	UFPs [#/cm³]	3,58 (-4,33 to 11,49)	-	-	-
	FP_{03-1} [#/cm³]	**-8,62 (-15,06 to -2,18)***	-8,19 (-17,14 to 0,75)	-8,52 (-18,97 to 1,93)	-9,46 (-20,81 to 1,88)
	$FP_{1-2.5}$ [#/cm³]	-3,35 (-9,99 to 3,29)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-4,16 (-9,61 to 1,29)	-	-	-
TP [ms²]	UFPs [#/cm³]	-4,29 (-15,54 to 8,47)	-	-	-
	FP_{03-1} [#/cm³]	-7,89 (-16,92 to 2,11)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-4,91 (-13,83 to 4,92)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-0,37 (-8,77 to 8,81)	-	-	-
LF/HF	UFPs [#/cm³]	0,78 (-13,09 to 14,65)	-	-	-
	FP_{03-1} [#/cm³]	-0,79 (-3,79 to 2,21)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-2,06 (-4,96 to 0,84)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-4,2 (-13,9 to 5,5)	-	-	-
HF [ms²]	UFPs [#/cm³]	-1,11 (-20,27 to 22,65)	-	-	-
	FP_{03-1} [#/cm³]	-3,12 (-19,1 to 16,02)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	5,34 (-11,25 to 25,03)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	8,24 (-6,94 to 25,89)	-	-	-
HF n.u.	UFPs [#/cm³]	1,88 (-7,71 to 12,47)	-	-	-
	FP_{03-1} [#/cm³]	2,15 (-5,99 to 10,99)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	5,58 (-2,57 to 14,41)	-	-	-

	$CP_{2,5-10}$ [#/cm^3]	3 (-3,88 to 10,38)	-	-	-
LF [ms^2]	UFPs [#/cm^3]	-5,25 (-18,55 to 10,22)	-	-	-
	FP_{03-1} [#/cm^3]	-6,6 (-17,67 to 5,96)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-2,47 (-13,55 to 10,02)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	1,09 (-9,14 to 12,48)	-	-	-
LF n.u.	UFPs [#/cm^3]	-2,3 (-7,38 to 3,05)	-	-	-
	FP_{03-1} [#/cm^3]	-0,97 (-5,31 to 3,58)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-2,73 (-6,87 to 1,6)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	**-4,43 (-7,85 to -0,88)***	-4,22 (-9,94 to 1,86)	**-7,4 (-12,69 to -1,79)***	-0,26 (-6,83 to 6,76)
VLF [ms^2]	UFPs [#/cm^3]	**-23,02 (-42,96 to -3,09)***	-16,56 (-48,88 to 15,77)	**-29,93 (-55,09 to -4,77)***	-7,84 (-55,7 to 40,01)
	FP_{03-1} [#/cm^3]	**-21,8 (-38,57 to -5,03)***	-21,52 (-44,8 to 1,76)	-22,69 (-49,8 to 4,42)	-21,19 (-51,06 to 8,69)
	$FP_{1-2.5}$ [#/cm^3]	**-17,71 (-34,68 to -0,75)***	-16,77 (-43,22 to 9,68)	-18,4 (-45,5 to 8,69)	-18,12 (-46,42 to 10,18)
	$CP_{2,5-10}$ [#/cm^3]	-12,65 (-26,65 to 1,34)	-	-	-

Notes: * = p < 0,05; ° = statistical significance borderline, p < 0,07

<u>TABLE 8-XIV</u> PERCENT CHANGES IN NIGHT-TIME HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE IN SUBJECTS WITH HIGH HSCRP LEVELS (HSCRP > 1,95 MG/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	40	13	17	10
HR [bpm]	UFPs [#/cm^3]	-0,46 (-3,05 to 2,13)	-	-	-
	FP_{03-1} [#/cm^3]	0,48 (-1,88 to 2,83)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	-1,16 (-3,08 to 0,76)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	0,55 (-1,49 to 2,6)	-	-	-
SDNN [ms]	UFPs [#/cm^3]	1,29 (-6,49 to 9,06)	-	-	-
	FP_{03-1} [#/cm^3]	-4,48 (-11,56 to 2,6)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	2,24 (-3,77 to 8,25)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	-0,94 (-7,09 to 5,2)	-	-	-
rMSSD [ms]	UFPs [#/cm^3]	-4,17 (-17,76 to 11,66)	-	-	-
	FP_{03-1} [#/cm^3]	2,59 (-10,74 to 17,91)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	5,76 (-5,82 to 18,77)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	9,77 (-2,23 to 23,24)	-	-	-
PNN50 [%]	UFPs [#/cm^3]	-17,25 (-43,1 to 20,33)	-	-	-
	FP_{03-1} [#/cm^3]	3,14 (-27,12 to 45,95)	-	-	-
	$FP_{1-2.5}$ [#/cm^3]	2,08 (-23,91 to 36,94)	-	-	-
	$CP_{2,5-10}$ [#/cm^3]	19,35 (-10,77 to 59,64)	-	-	-

SDANN [ms]	UFPs [#/cm³]	9,3 (-1,78 to 20,37)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	-7,98 (-18,26 to 2,31)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	1,95 (-7,57 to 11,47)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-1,64 (-10,08 to 6,8)	-	-	-
TP [ms²]	UFPs [#/cm³]	-5,5 (-17,47 to 8,19)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	2,91 (-8,7 to 15,99)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	2,03 (-7,4 to 12,41)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	6,35 (-4,37 to 18,28)	-	-	-
LF/HF	UFPs [#/cm³]	7,81 (-11,6 to 27,23)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	8,43 (-9,97 to 26,82)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	-2,82 (-7,44 to 1,79)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-4,64 (-19,24 to 9,96)	-	-	-
HF [ms²]	UFPs [#/cm³]	-8,6 (-33,21 to 25,07)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	6,73 (-19,72 to 41,88)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	12,98 (-10,95 to 43,33)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	23,85 (-2,08 to 56,64)	-	-	-
HF n.u.	UFPs [#/cm³]	0,16 (-13,7 to 16,24)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	0,48 (-12,6 to 15,53)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	6,27 (-5,83 to 19,92)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	8,11 (-3,38 to 20,97)	-	-	-
LF [ms²]	UFPs [#/cm³]	-11,09 (-24,97 to 5,34)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	6,95 (-7,87 to 24,16)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	0,88 (-10,99 to 14,34)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	8,42 (-5,09 to 23,85)	-	-	-
LF n.u.	UFPs [#/cm³]	-4,33 (-12,26 to 4,33)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	-2,89 (-10,51 to 5,38)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	-4,99 (-11,43 to 1,93)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-4,85 (-10,9 to 1,61)	-	-	-
VLF [ms²]	UFPs [#/cm³]	**-25,88 (-51,62 to -0,13)***	-23,8 (-65,71 to 18,1)	**-34,31 (-67,57 to -1,06)***	-5,05 (-60,43 to 50,34)
	$FP_{03\text{-}1}$ [#/cm³]	-8,99 (-32,74 to 14,76)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	-1,89 (-21,37 to 17,59)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-6,91 (-27,87 to 14,04)	-	-	-

Notes: *p < 0,05; °Borderline statistical significance (p < 0,07).

TABLE 8-XV PERCENT CHANGES IN NIGHT-TIME HRV INDICES ASSOCIATED WITH AN INTERQUARTILE RANGE INCREASE IN DAILY PARTICLES EXPOSURE IN SUBJECTS WITH LOW HSCRP LEVELS (HSCRP < 1,95 MG/L).

		Total Group	**"Healthy" Group**	**Heart Group**	**Lung Group**
		β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)	β % change (95% C.I.)
	Subjects [n]	39	14	17	8
HR [bpm]	UFPs [#/cm³]	-1,44 (-4,53 to 1,66)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	-0,84 (-3,59 to 1,9)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	-1 (-3,85 to 1,84)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-0,06 (-2,35 to 2,24)	-	-	-
SDNN [ms]	UFPs [#/cm³]	-1,59 (-12,49 to 9,31)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	**-10,35 (-19,56 to -1,14)***	-8,79 (-25,09 to 7,52)	-9,53 (-21,83 to 2,77)	-14,21 (-33,19 to 4,77)
	$FP_{1\text{-}2.5}$ [#/cm³]	**-11,04 (-20,51 to -1,56)***	-6,7 (-23,6 to 10,2)	-7,48 (-19,9 to 4,94)	**-23 (-40,2 to -5,8)***
	$CP_{2,5\text{-}10}$ [#/cm³]	**-7,27 (-15,09 to 0,55)°**	-3,75 (-21,46 to 13,96)	-8,45 (-18,88 to 1,98)	-7,12 (-23,73 to 9,5)
rMSSD [ms]	UFPs [#/cm³]	14,62 (-2,68 to 34,98)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	1,8 (-12,27 to 18,13)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	4,61 (-9,76 to 21,28)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	2,46 (-9,49 to 15,98)	-	-	-
PNN50 [%]	UFPs [#/cm³]	30,65 (-17,67 to 107,33)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	1,01 (-32,92 to 52,1)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	9,21 (-27,96 to 65,55)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	5,92 (-24,73 to 49,05)	-	-	-
SDANN [ms]	UFPs [#/cm³]	-4,1 (-17,28 to 9,08)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	-10,25 (-21,46 to 0,95)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	**-12,52 (-24,23 to -0,82)***	-8,18 (-29,03 to 12,67)	-10,14 (-25,76 to 5,49)	**-22,05 (-43,64 to -0,46)***
	$CP_{2,5\text{-}10}$ [#/cm³]	-7,42 (-16,88 to 2,04)	-	-	-
TP [ms²]	UFPs [#/cm³]	4,23 (-16,91 to 30,75)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	-7,81 (-24,64 to 12,78)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	-9 (-25,77 to 11,56)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	-6,81 (-21,14 to 10,12)	-	-	-
LF/HF	UFPs [#/cm³]	-17,23 (-37,67 to 3,2)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	**-22,72 (-39,91 to -5,54)***	**-55,54 (-82,17 to -28,91)***	-11,66 (-32,81 to 9,49)	-15,42 (-45,33 to 14,48)
	$FP_{1\text{-}2.5}$ [#/cm³]	**-4,27 (-7,55 to -1)***	**-6,84 (-12,91 to -0,77)***	**-4,55 (-8,99 to -0,12)***	-1,03 (-7,03 to 4,98)
	$CP_{2,5\text{-}10}$ [#/cm³]	-9,37 (-25,07 to 6,32)	-	-	-
HF [ms²]	UFPs [#/cm³]	27,21 (-6,71 to 73,46)	-	-	-
	$FP_{03\text{-}1}$ [#/cm³]	5,4 (-20,89 to 40,43)	-	-	-
	$FP_{1\text{-}2.5}$ [#/cm³]	14,83 (-12,88 to 51,37)	-	-	-
	$CP_{2,5\text{-}10}$ [#/cm³]	4,14 (-18,02 to 32,29)	-	-	-
n ·	UFPs [#/cm³]	11,51 (-0,96 to 25,54)	-	-	-

	FP_{03-1} [#/cm³]	**13,87 (2,96 to 25,93)***	**27,32 (7,65 to 50,59)***	11,76 (-2,11 to 27,59)	6,46 (-11,62 to 28,23)
	$FP_{1-2.5}$ [#/cm³]	**14,29 (3,67 to 26)***	**23,49 (3,17 to 47,8)***	**14,96 (0,81 to 31,09)***	4,52 (-12,51 to 24,87)
	$CP_{2,5-10}$ [#/cm³]	5,24 (-4,04 to 15,42)	-	-	-
LF [ms²]	UFPs [#/cm³]	10,39 (-15,51 to 44,22)	-	-	-
	FP_{03-1} [#/cm³]	-5,72 (-25,88 to 19,91)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-4,32 (-24,9 to 21,89)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-3,6 (-21,08 to 17,74)	-	-	-
LF n.u.	UFPs [#/cm³]	-3,55 (-9,34 to 2,61)	-	-	-
	FP_{03-1} [#/cm³]	-0,23 (-5,68 to 5,53)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	-3,17 (-8,25 to 2,2)	-	-	-
	$CP_{2,5-10}$ [#/cm³]	-2,58 (-6,98 to 2,03)	-	-	-
VLF [ms²]	UFPs [#/cm³]	-4,56 (-23,41 to 14,3)	-	-	-
	FP_{03-1} [#/cm³]	-11,57 (-28,04 to 4,9)	-	-	-
	$FP_{1-2.5}$ [#/cm³]	**-19,49 (-35,93 to -3,04)***	-2,29 (-31,16 to 26,58)	-18,48 (-39,67 to 2,71)	**-37,74 (-67,09 to -8,4)***
	$CP_{2,5-10}$ [#/cm³]	**-14,22 (-27,59 to -0,85)***	5,52 (-24,33 to 35,36)	**-21,01 (-38,41 to -3,6)***	-13,02 (-40,79 to 14,76)

Notes: *$p < 0,05$; °Borderline statistical significance ($p < 0,07$).

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