Acta Medica Mediterranea, 2014, 30: 347

CARDIOVASCULAR EFFECTS OF OCCUPATIONAL EXPOSURE TO URBAN AIRBORNE POLLUTION ON A GROUP OF NEWSAGENTS IN THE CITY OF PALERMO

PAOLA DE MARCHIS[1], MARIA GABRIELLA VERSO[2], FABIO TRAMUTO[2], DOMENICA MATRANGA[2], FRANCESCO VITALE[2], DIEGO PICCIOTTO[2]

[1]Department of Science for Health promotion, Maternal and Child Health, Medicine Faculty, University of Palermo - [2]Department of Science for Health promotion, Maternal and Child Health, Medicine Faculty, University of Palermo, Italy

ABSTRACT

***Aims**: To verify the possible correlation between exposure to airborne particulate matter the average size less than 10 μm (PM 10) of a group of newsagents working in kiosks in Palermo and evidence of carotid intimal thickening.*

***Materials and methods**: data were collected relating to environmental monitoring of airborne pollutants. We have selected a sample of newsagents, who were submitted to some clinical investigations, including the carotid echo-color doppler examination.*

***Results**: The results show no correlation between the location of the kiosks, and the presence of intimal thickening.*

***Conclusion**: Exposition to urban pollutants in Palermo is likely homogenous in the different areas and can be considered an ubiquitous atherogenic risk factor.*

***Key words**: Air pollution, arterial intimal thickening, particulate air matter, PM10, cardiovascular diseases.*

***Received** January 18, 2014; **Accepted** January 24, 2014*

Introduction

Air pollution is a generic risk factor for human health, especially for people living in urban areas. This environmental issue is an important occupational risk factor for workers who operate in urban setting for several hours a day. Air pollution is a heterogeneous mixture of gases, liquids and particulate matter. The most important pollutants derived from fossil fuel combustion, as vehicle exhaust and industrial emissions. Many pollutants are responsible of pathological effects on human health. First of all the atmospheric particulate matter, sulfur oxides, ozone, carbon monoxide, benzene, polycyclic aromatic hydrocarbons and volatile organic compounds[1, 2]. Several studies show a strong statistical association between chronic exposition to airborne pollutants and cardiovascular diseases, including myocardial ischemia and infarctions, heart failure, arrhythmias, strokes and increased cardiovascular mortality.

Numerous epidemiologic and toxicological experiments show generally consistent associations between cardiovascular mortality and chronic exposure to particulate air pollution. A lot of research evidence the important role of air particulate on the progression of intimal thickness[3-14]. Some research conclude that exposition to air pollution is as a potential atherogenic risk factor and insert it between the traditionally known cardiovascular risk factors[8-9, 11]. Airborne particulate matter is composed of two fractions: fine particles, so-called "coarse particulate" (the average size between 2.5 and 10 μm), and ultra-fine, defined as "fine particulate" (dimensions less than 2.5 μm). Both fractions can damage arterial endothelium with different biological pathways. The particles inhaled in the bronchial tree, reach the lower respiratory ways, and stimulate at least three different mechanisms: activation of an inflammatory process with systemic oxidative stress, alteration of the balance of the autonomic nervous system and a potential direct

action on the arterial wall. Experimental studies show that PM 10 increases the expression of inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX -2) in endothelial cells and increases plasmatic levels of endothelin-1. In vitro tests also suggest an important role of alveolar macrophages, which, if exposed to atmospheric particulates, release cytokines stimulating the bone marrow to increase the production of leukocytes and platelets. These phenomena increase the progression of atherogenic injury on vascular endothelium[15-24]. Many scientists studied intimal thickening, as an important marker of preclinical atherosclerosis. Several prospective studies like the CHS, the Rotterdam and the ARIC Study, defined carotid intimal-media thickness (IMT) an important prognostic indicator of atherosclerosis evolution. It is used commonly like a positive predictive value of cerebral and hearth ischemic events[25-27].

The aim of this study is to evaluate the presence of subclinical atherosclerosis, by the ultrasound measurement of carotid IMT, on a group of newsagents working in outdoor kiosks inside the city of Palermo, who are occupationally exposed to urban pollutants airborne for several hours a day. It also aims to observe possible correlation between the IMT found and the exposure to different concentrations of PM10 in various areas of the city.

Material and methods

Environmental monitoring

The first phase of the study focused on the collection of data related to air monitoring in the urban area of the city of Palermo. We used the results of the monitoring carried out by A.M.I.A. (the local Agency for environmental management of the city of Palermo). We examined the time series from 01/01/2012 to 31/12/2012. The monitoring was carried out by 9 fixed gas detection stations, variously located in different areas of the city, all connected to a single processing center and data recording. The cabins are conform to the UNI EN ISO 9001:2000. In the figure number 1 we illustrated location and denomination of the cabins, in the urban context of the city.

The parameters measured by the control cabins are the daily average concentrations of sulfur dioxide (SO_2), the maximum value of the hourly averages recorded between 00:00 am and 24:00 pm for nitrogen dioxide (NO_2), the maximum value of the 8-hour averages calculated every hour between the hours of 00:00 and 24:00 of carbon monoxide (CO), the maximum values of the hourly averages and averages over 8 hours between 00:00 am and 24:00 pm of ozone (O_3), the daily and average annual concentrations of benzene and PM 10. All values are expressed in micrograms per cubic meter (μg/m3).

For each parameter we observed the number of exceedances of the limit value for the protection of human health for the year. We found a significant number of exceedances of limit values in the year only for PM10, and so we considered just this pollutant for the statistical analyses. The daily limit value for the protection of human health within 24 hours of PM 10 is 50 μg/m3, as defined by current italian legislation.

Examination of the sample

TWe have selected a sample of newsagents operating in outdoor kiosks in the city, aged 18-65 years, without known chronic degenerative diseases. Each newsagent worked for at least three years. We recruited the sample, with personal interviews. The questionnaire was designed to obtain information about working environment and organization, like location and surface of the kiosk, air conditioning devices, hours of work, weekly rest and eventual shifts, lunch break, vacations and sick leave. Every newsagent, was subjected to a medical examination. We investigated about familiar and personal cardiovascular risk factors, particularly smoking, eating habits, lifestyle and sedentary. During the physical examination we observed especially the cardiovascular system. Particular attention we paid to the possible presence of hearth and carotid murmurs. The sample was then subjected to a venous blood sampling for examining complete blood count, glycemia, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, creatinine, transaminases, gamma glutamyl transpeptidase (GGT), alkaline phosphatase. We also performed an urinalysis, with chemical-physical examination. For each subject we made also instrumental tests such as electrocardiogram and ultrasound examination of the neck arteries. The ultrasound study of the neck vessels was performed using the criteria suggested by the European society of Cardiology and Hypertension[28]. We examined the extracranial carotid arteries, using as a threshold value for IMT, the value of 0.9 mm, beyond which is defined as pathological. The examination was conducted with B-mode real-time ultrasound using a machine Toshiba 270 SS with a probe of 7.5 to 10.0 MHz. The power output, focus, depth

of measurement, and gain were standardized by using preset program incorporated within the software package of the ultrasound equipment. The IMT was defined as the distance between the echogenic line representing the intima-blood interface and the outer-echogenic line representing the adventitia junction. After freezing the image, the measurement was made with electronic calipers. Patients were examined in the supine position. The IMT was measured on the rear wall of the common carotid artery at the distance of 1 cm from the bifurcation. We made at least three projections and we used the mean value.

Statistical analysis

The association between IMT and enviromental and systemic variables was assessed using the $\chi 2$ test or Fisher's exact test, as appropriate. A p value ≤ 0:05 was considered statistically significant. To measure the association level, crude odds ratio (OR) and the corresponding 95% test-based Confidence Interval (CI) were calculated. The newsagents were divided into eight groups, by the proximity with the most important gas monitoring stations, in multilevel logistic regression model. Variables tested for inclusion in the multivariate model were those significantly associated with intimal thickening at $p \leq 0.05$ for the univariate analysis, using manual forward selection. In order to assess the association between pollutants and IMT, the average annual of PM10 was included in the analysis too. The adjusted OR, with 95 % confidence interval (CI), was provided for all independent variables included in the models. Statistical analysis was performed using Stata Software MP/11.2.

Results

Environmental monitoring

The collection of data related to environmental monitoring has shown a number of exceedances of the limit values for the protection of human health of PM 10 illustrated in the table 1.

Di Blasi	Castelnuovo	Giulio Cesare	Belgio	Torrelunga	CEP	Indipendenza	Unità d'Italia	Boccadifalco
58	33	33	15	11	7	6	4	7

Table 1: Number of exceedances of the annual limit value for the protection of human health
of PM 10 for each cabin (unite of measure: μg/m3). Daily limit value for the protection of human health in 24 hours: 50 $\mu g/m^3$.

The average annual concentration of PM 10 is illustrated in the table 2.

Di Blasi	Castelnuovo	Giulio Cesare	Belgio	Torrelunga	CEP	Unità d'Italia	Indipedenza	Boccadifalco
40	36	35	30	30	29	29	4	15

Table 2: Annual average of PM 10 ($\mu g/m^3$) for each cabin.

Characteristics of the sample

The selected sample is composed of 67 newsagents, 12 women (17.9%) and 55 men (82.1%), with a mean age of 51.2 ± 8.1 years and mean seniority working of 19.4 ± 9.9 years. 56 subjects (83.6%) spend more than 12 hours a day inside the kiosk, the rest of the sample, amounting to 11 subjects (16.4%), almost all female, spend 4-6 hours in the kiosk. 20 subjects were smokers (29.8%), 47 subjects (70.2 %) were non-smokers or ex-smokers over 10 years. We observed hypercholesterolemia (total cholesterol in the blood above 220 mg/dl) in 19 subjects (28.4 %), with a consensual increase in LDL cholesterol levels in 7 of them. Only in two cases (3%) was detected isolated hypertriglyceridemia (triglyceride in the blood above 150 mg/dl). We found 15 cases (22.4%) of elevated blood pressure levels and 14 cases (20.9%) of overweight, defined as BMI greater than 25. Finally, 14 subjects (20.9%) practiced regular physical activity at least two times a week.

The echo-color doppler results are shown in the table 3.

No alterations	Intimal thickening	Atherosclerotic plaque (obstructing the arterial lumen by up to 40%)	Atherosclerotic plaque (obstructing the arterial lumen by up to 60%)
38 (56,7%)	23 (34,3%)	3 (4,5%)	3 (4,5%)

Table 3: number of alterations found by echo-color doppler ultrasound.

The number of kiosks evaluated for each control cabin of reference is shown in tab. 4.

Di Blasi	Castelnuovo	Giulio Cesare	Belgio	Torrelunga	CEP	Unità d'Italia	Indipedenza	Boccadifalco
3 (4,5%)	15 (22,4%)	17 (25.4%)	7 (10.4%)	4 (6%)	2 (3%)	9 (13,4%)	7 (10,4%)	3 (4,5%)

Table 4: Number of kiosks observed for the reference cabin.

The results of the statistical analysis are shown in Table 5 and 6.

As shown in the table 5 we observed a statistical correlation between carotid IMT and the age of the subjects, with a lack of statistical significance: crude OR 2.72, p 0.04, 95% CI (0.97-7.68). We found a weak correlation with the daily exposure and also a statistically significant correlation between the IMT and blood

pressure levels: crude OR 5.20, p 0.008, 95% IC (1.7-24.9). The multivariate analysis is illustrated in the table 6. It confirms these results and shows no association between the alterations observed and the levels of PM10.

Variable	n	With Intimal thickness	%	Crude OR	95% CI	P
Age						
≤51.2	37	12	32.4	1.00		0.046
>51.2	30	17	56.7	2.72	[0.97; 7.68]	
Smoking						
No	47	20	42.6	1.00		0.853
Yes	20	9	45.0	1.10	[0.33; 3.59]	
Sedentary						
No	14	5	35.7	1.00		0.520
Yes	53	24	45.3	1.49	[0.38; 6.42]	
Seniority						
≤19.4	35	12	34.3	1.00		0.120
>19.4	32	17	53.1	2.17	[0.79; 5.97]	
Daily exposure time						
Half a day	11	2	18.2	1.00		0.066
All the day	56	27	48.2	4.19	[0.75; 42.46]	
Total Cholesterol						
≤220	48	20	41.7	1.00		0.671
>220	19	9	47.4	1.26	[0.38; 4.17]	
LDL Cholesterol						
≤160	60	24	40.0	1.00		0.112
>160	7	5	71.4	3.75	[0.55; 41.58]	
Triglycerides						
≤200	65	28	43.1	1.00		0.846
>200	2	1	50.0	1.32	[0.02;106.49]	
BMI						
≤25	53	25	47.2	1.00		
>25	14	4	28.6	0.45	[0.09; 1.83]	0.212
Blood Pressure						
Normal	52	18	34.6	1.00		0.008
Hypertension	15	11	73.3	5.20	[1.27; 24.99]	
In bold: statistically significant						

Table 5: Number of kiosks observed for the reference cabin.

Characteristics of the newsagents [a)]	OR	95%CI	p
Age			
>51.2 vs ≤51.2	2.20	[0.77-6.27]	0.143
Blood pressure			
Hypertension vs Normal	4.37	[1.17-16.30]	0.028
Characteristics of the pollution stations			
PM10	1.00	[0.90; 1.12]	0.965

a) = Only variables significant in the univariate analysis are included. In bold: statistically significant

Table 6: Intimal thickening by characteristics of newsagents and pollution stations: multivariate analysis.

Discussion

The data provided by the A.M.I.A. emphasize a high level of diffuse pollution, especially of airborne particulate. The levels of the other pollutants are not relevant for human health and so we have not considered in the present study. The particulate matter origin mainly from exhaust gas veicholar. Other gases, such as nitrogen dioxide and sulfur dioxide, benzene and carbon monoxide, originate in part also from industrial emissions, almost absent in the city and probably are less persistent in the atmosphere. Palermo is also characterized by particular geographical connotation, included in a semi-circular basin, the so-called "golden valley", bounded on one side by the sea and on the other side by a chain of mountains, as we can see in Figure 1.

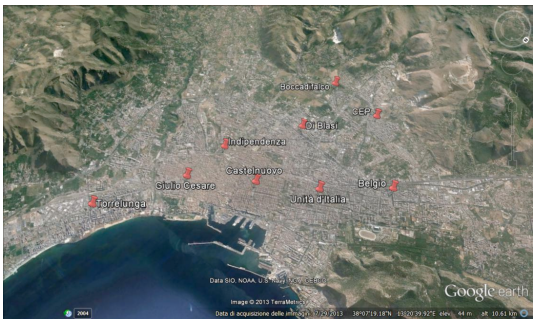

Fig. 1: Location and name of control cabins in the urban context.

Industrial installations are located to the east and west of the city, mostly out of the town. Inside the "Golden Valley" weather conditions are quite stable, with consequent impact on the levels of airborne pollution. We can affirm that, despite the number of exceedances of the level of protection for human health of PM10 was different in various units, the variability of annual averages for each unit is insignificant. If we exclude the unit Boccadifalco, very peripheral, and Castelnuovo, in the shopping center of the city, the others cabins have variable annual average daily between 29 and 36 μg/m3. This is a slight difference, in absolute terms. The lack of variability in the concentrations of pollutants, the proximity crow flies of various newsstands and the particular geography of the site, make the concentrations of PM10 quite homogeneous. So all urban areas have a high level of pollution. This could explain the absence of statistically significant correlation between intimal thickening and the locations of the kiosks. Moreover a difference of a few micrograms per cubic meter probably cannot determine a difference in the oxidative damage to the vascular endothelium. We remember that the IMT is a multifactorial phenomenon and with a slow progression. The results obtained show an overall percentage of intimal changes amounted to 43.3%. There was, as expected, a statistically significant correlation between elevated blood pressure and the occurrence of IMT. If we exclude from the study sample hypertensive subjects, the percentage of intimal damage, including thickening and atherosclerotic plaques, appear to be 34.6%. This data should be compared with a control population. Because we have not at this stage of the study of an appropriate control population, we can compare our outcomes with the results of the important cross-sectional study, defined "Heart Project"[29-31], by the Italian Higher Institute of Health (ISS). The "Hearth Project", examined people aged 18-65 years, with a low cardiovascular risk. It was founded approximately 21% of the examined people with artery endothelium damage, of which 13% it is represented by atherosclerotic plaques and 8% by intimal thickening. The results of the ISS were found in a population comparable to our study sample, except for occupational exposure to outdoor urban environment. Few categories of workers in Italy spend the majority of the day outdoors in areas with high vehicle traffic, like newsagents. In the study sample over the 80% of the subjects remains within the newsstands for a time greater than 12 hours a day. The "Hearth Project" doesn't make a regional distribution of endothelium damage percentage, but we know that a decreasing north-south gradient, documented throughout Europe, exist, as it is demonstrated by numerous studies, such as the IMPROVE Study[32, 3

Conclusion

The data provided by the A.M.I.A. emphasize a high level of diffuse pollution, especially of airborne particulate. The levels of the other pollutants are not relevant for human health and so we have not considered in the present study. The particulate matter origin mainly from exhaust gas veicholar. Other gases, such as nitrogen dioxide and sulfur dioxide, benzene and carbon monoxide, originate in part also from industrial emissions, almost absent in the city and probably are less persistent in the atmosphere. Palermo is also characterized by particular geographical connotation, included in a semi-circular basin, the so-called "golden valley2, bounded on one side by the sea and on the other side by a chain of mountains, as we can see in Figure 1. Industrial installations are located to the east and west of the city, mostly out of the town. Inside the "Golden Valley" weather conditions are quite stable, with consequent impact on the levels of airborne pollution. We can affirm that, despite the number of exceedances of the level of protection for human health of PM10 was different in various units, the variability of annual averages for each unit is insignificant. If we exclude the unit Boccadifalco, very peripheral, and Castelnuovo, in the shopping center of the city, the others cabins have variable annual average daily between 29 and 36 μg/m3. This is a slight difference, in absolute terms. The lack of variability in the concentrations of pollutants, the proximity crow flies of various newsstands and the particular geography of the site, make the concentrations of PM10 quite homogeneous. So all urban areas have a high level of pollution. This could explain the absence of statistically significant correlation between intimal thickening and the locations of the kiosks. Moreover a difference of a few micrograms per cubic meter probably cannot determine a difference in the oxidative damage to the vascular endothelium. We remember that the IMT is a multifactorial phenomenon and with a slow progression. The results obtained show an overall percentage of intimal changes amounted to 43.3%. There was, as expected, a statistically significant correlation between elevated blood pressure and the occurrence of IMT. If we exclude from the study sample hypertensive subjects, the percentage of intimal damage, including thickening and atherosclerotic plaques, appear to be 34.6%. This data should be compared with a control population. Because we have not at this stage of the study of an appropriate control population, we can compare our outcomes with the results of the important cross-sectional study, defined "Heart Project"[29-31], by the Italian Higher Institute of Health (ISS). The "Hearth Project", examined people aged 18-65 years, with a low cardiovascular risk. It was founded approximately 21% of the examined people with artery endothelium damage, of which 13% it is represented by atherosclerotic plaques and 8% by intimal thickening. The results of the ISS were found in a population comparable to our study sample, except for occupational exposure to outdoor urban environment. Few categories of workers in Italy spend the majority of the day outdoors in areas with high vehicle traffic, like newsagents. In the study sample over the 80% of the subjects remains within the newsstands for a time greater than 12 hours a day. The "Hearth Project" doesn't make a regional distribution of endothelium damage percentage, but we know that a decreasing north-south gradient, documented throughout Europe, exist, as it is demonstrated by numerous studies, such as the IMPROVE Study[32, 33].

References

1) Zheng M, Zhao X, Cheng Y, Yan C, Shi W, Zhang X, Weber RJ, Schauer JJ, Wang X, Edgerton ES. *Sources of primary and secondary organic aerosol and their diurnal variations*. J Hazard Mater. 2013 Oct 28. pii: S0304-3894(13)00796-6. doi: 10.1016/j.jhazmat.2013.10.047.
2) Koulova A, Frishman WH. *Air pollution exposure as a risk factor for cardiovascular disease morbidity and mortality*. Cardiol Rev. 2014. Jan-Feb; 22(1): *30-6*.
3) Balduzzi M. *Biological effects of PM10 relevant to human health*. Ann Ist Super Sanità 2003; 39 (3): *411-417*.
4) Feng J, Yang W. *Effects of particulate air pollution on cardiovascular health: a population health risk assessment*. PLoS One. 2012;7(3):e33385. Epub 2012 Mar 14.
5) Orru H, Jõgi R, Kaasik M, Forsberg B. *Chronic Traffic-Induced PM Exposure and Self-Reported Respiratory and Cardiovascular Health in the RHINE Tartu Cohort. International Journal of Environmental Research and Public Health*. ISSN 1660-4601 www.mdpi.com/journal/ijerph
6) Qin G, Lü JY. *Association between particulate matter air pollution and atherosclerosis*. Zhonghua Xin Xue Guan Bing Za Zhi. 2011 Mar; 39(3): *282-4*.
7) Tonne C, Yanosky JD, Beevers S, Wilkinson P, Kelly FJ. *PM mass concentration and PM oxidative potential in relation to carotid intima-media thickness*. P. Epidemiology. 2012 May; 23(3): *486-94*.
8) Bauer M, Moebus S, MÃ¶hlenkamp S, Dragano N, Nonnemacher M, Fuchsluger M, Kessler C, Jakobs H, Memmesheimer M, Erbel R, JÃckel KH, Hoffmann B; *HNR Study Investigative Group. Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study*. J Am Coll Cardiol. 2010 Nov 23; 56(22): *1803-8*.

9) Brook RD. *Cardiovascular effects of air pollution*. Clin Sci (Lond). 2008 Sep; 115(6): *175-87*.
10) Delfino RJ, Sioutas C, Malik S. *Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health*. Environ Health Perspect. 2005 Aug; 113(8): *934-46*.
11) Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. *Particulate air pollution induces progression of atherosclerosis*. J Am Coll Cardiol. 2002 Mar 20; 39(6): *935-42*.
12) Nishiwaki Y, Michikawa T, Takebayashi T, Nitta H, Iso H, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group. *Long-term exposure to particulate matter in relation to mortality and incidence of cardiovascular disease: the JPHC Study*. J Atheroscler Thromb. 2013; 20(3): *296-309*. Epub 2012 Nov 22.
13) Langrish JP, Mills NL. *Air pollution and mortality in Europe*. Lancet. 2013 Dec 6. pii: S0140-6736(13)62570-2.
14) Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, Samoli E, Touloumi G, Burnett RT, Krewski D, Ramsay T, Dominici F, Peng RD, Schwartz J, Zanobetti A; HEI Health Review Committee. *Air pollution and health: a European and North American approach (APHENA)*. Res Rep Health Eff Inst. 2009 Oct; (142): *5-90*.
15) Grahame TJ, Schlesinger RB. *Oxidative Stress-Induced Telomeric Erosion as a Mechanism Underlying Airborne Particulate Matter-Related Cardiovascular Disease*. Part Fibre Toxicol. 2012 Jun 19; 9(1): *21*.
16) Lee CC, Huang SH, Yang YT, Cheng YW, Li CH, Kang JJ. *Motorcycle exhaust particles up-regulate expression of vascular adhesion molecule-1 and intercellular adhesion molecule-1 in human umbilical vein endothelial cells*. Toxicol In Vitro. 2012 Jun; 26(4): *552-60*.
17) Campen MJ, Lund A, Rosenfeld M. *Mechanisms linking traffic-related air pollution and atherosclerosis*. Curr Opin Pulm Med. 2012 Mar; 18(2): *155-60*.
18) Shrey K, Suchit A, Deepika D, Shruti K, Vibha R. *Air pollutants: the key stages in the pathway towards the development of cardiovascular disorders*. Environ Toxicol Pharmacol. 2011 Jan; 31(1): *1-9*.
19) Franchini M, Mannucci PM. *Thrombogenicity and cardiovascular effects of ambient air pollution*. Blood. 2011 Sep 1; 118(9): *2405-12*.
20) Lund AK, Lucero J, Harman M, Madden MC, McDonald JD, Seagrave JC, Campen MJ. *The oxidized low-density lipoprotein receptor mediates vascular effects of inhaled vehicle emissions*. Am J Respir Crit Care Med. 2011 Jul 1; 184(1): *82-91*.
21) Poursafa P, Kelishadi R. *Air pollution, platelet activation and atherosclerosis*. Inflamm Allergy Drug Targets. 2010 Dec; 9(5): *387-92*.
22) Du Y, Navab M, Shen M, Hill J, Pakbin P, Sioutas C, Hsiai TK, Li R. *Ambient ultrafine particles reduce endothelial nitric oxide production via S-glutathionylation of eNOS*. Biochem Biophys Res Commun. 2013 Jul 5; 436(3): *462-6*.
23) Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. *Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease*. Circulation. 2004 Jan 6; 109(1): *71-7*.
24) Ohlson CG, Berg P, Bryngelsson IL, Elihn K, Ngo Y, Westberg H, Sjögren B. *Inflammatory markers and exposure to occupational air pollutants*. Inhal Toxicol. 2010 Nov; 22(13): *1083-90*.
25) Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, Ballantyne CM. *Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study*. Eur Heart J. 2012 Jan; 33(2): *183-90*.
26) Linda P. Fried, Nemat O. Borhani, Paul Enright, Curt D. Furberg, Julius M. Gardin, Richard A. Kronmal, Lewis H. Kuller, Teri A. Manolio, Maurice B. Mittelmark, Anne Newman, Daniel H. O'Leary, Bruce Psaty, Pentti Rautaharju, Russell P. Tracy, Philip G. Weiler. *The cardiovascular health study: Design and Rationale*. Ann Epidemiol 1991;1: *263-276*.
27) Elias-Smale SE, Kavousi M, Verwoert GC, Koller MT, Steyerberg EW, Mattace-Raso FU, Hofman A, Hoeks AP, Reneman RS, Witteman JC. *Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study*. Eur J Prev Cardiol. 2012 Aug; 19(4): *698-705*.
28) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. *2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension*. Blood Press. 2013 Dec 20.
29) Muggeo V.M.R, Lovison G. Mortality, *Temperature and Air Pollution in Palermo, Italy*. Working Paper Graspa n. 12
30) Palmieri L, Rielli R, Demattè L, Donfrancesco C, Ciccarelli P, De Sanctis Caiola P, Dima F, Lo Noce C, Brignoli O, Cuffari A, Giampaoli S. *CUORE project: implementation of the 10-year risk score*. Eur J Cardiovasc Prev Rehabil. 2011 Aug; 18(4): *642-9*.
31) Donfrancesco C, Palmieri L, Vanuzzo D, Panico S, Cesana G, Ferrario M, Pilotto L, Giampaoli S. *Italian cardiovascular mortality charts of the CUORE Project: are they comparable with the SCORE charts?*. G Ital Cardiol (Rome). 2010 Feb; 11(2): *148-53*.
32) Baldassarre D, Veglia F, Hamsten A, Humphries SE, Rauramaa R, de Faire U, Smit AJ, Giral P, Kurl S, Mannarino E, Grossi E, Paoletti R, Tremoli E; IMPROVE Study Group. *Progression of carotid intima-media thickness as predictor of vascular events: results from the IMPROVE study*. Arterioscler Thromb Vasc Biol. 2013 Sep; 33(9): *2273-9*.
33) Biggeri, A., et al. *Particulate air pollution and health in Italy: A meta-analysis of 8 Italian cities*. Epidemiology. 2001 Jul; 12: *530*.

Request reprints from:
PAOLA DE MARCHIS
Via Francesco Lo Jacono n. 36
90144, Palermo
(Italy)