# Blood and urinary nickel from urban pollution and blood pressure

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**Summary**

***Background:*** **outdoor workers are daily exposed to chemical agents including nickel.**
***Objectives:*** **the aim of the study is to evaluate the relationship between nickel and blood pressure in outdoor workers.**
***Methods:*** **a total of 349 subjects of both sexes were enrolled in the study. We evaluated the dose of blood and urinary nickel. Blood pressure in supine and standing positions was measured in all subjects.**
**Statistical analysis (Pearson correlation coefficient, multiple linear regression analysis and Kolmogorov-Smirnov test) was performed using the software SPSS® Advanced Statistical™ 10.0 (SPSS Science, Chicago, IL).**
***Results:*** **serum and urinary nickel don't show any probative correlation with blood pressure.**
***Conclusions:*** **the overall results of our study cannot prove that the exposure to nickel has a real effect on blood pressure, however some partial results lead to carry on further research.**

*KEY WORDS: nickel, air pollution/adverse effects, blood pressure monitoring.*

## Introduction

Exposure to pollution from the urban traffic is a significant risk factor for the health of workers, being a cause of some deadly diseases (1, 2). Several studies have observed an association between acute or chronic exposure to the pollutants present in urban traffic such as particulate matter (PM), nitrogen oxide ($NO_2$), ozone ($O_3$), carbon monoxide (CO) and sulphur dioxide ($SO_2$), and increased risk of cardiovascular morbidity and mortality (3-9). These include coronary artery disease (10, 11), arrhythmias (12, 13), myocardial infarction (14-17), heart failure (17, 18) and an increase in blood pressure (19-30).
Among the urban pollutants the particulate matter (PM), together with the various adsorbed substances, is considered to be mainly responsible for the cardiovascular effects described above. In humans, inhalation exposure to PM decreases the heart rate variability (31-33), causes endothelial and autonomic dysfunction (34) and accelerates the progression of atherosclerosis (35-38). The mechanisms of cardiotoxicity induced by air pollution include the increase in oxygen reactive species followed by activation of pro-inflammatory and pro-thrombotic pathways (39-42).
Among the many urban pollutants adsorbed on PM, metals above all nickel (Ni) are included (43-44). The Ni present in urban air originates from natural sources and anthropogenic sources such as processes of extraction and refining of nickel, coal combustion, vehicular traffic, domestic heating, waste incineration (45); nickel is contained as an additive in unleaded gasoline (46, 47), as a catalyst in the catalytic converter (48, 49), in paints, in solvents (50) and in some pesticides (51).
Spending most of their time in urban areas for occupational reasons outside workers (such as firefighters, police drivers, newsagents, taxi drivers, etc. ) are exposed to a number of chemicals daily (52-65). Using specific biomarkers, it is possible to value work exposure to many pollutants (66).
The aim of this study is to evaluate a group of outdoor workers of a major Italian city to establish whether levels of blood and urinary nickel can be related to blood pressure.

## Materials and methods

The study was conducted on a sample of 349 individuals (229 males and 120 females), all employees in outdoor activities for the Municipal Police of a major Italian city, from May 2006 to March 2010. None of the urban police officers was provided with personal equipment for the protection against dust and fumes from traffic pollution.

From a total of approximately 1000 outdoor workers, we selected randomly 349 employees from different areas of the town, considered the most representative as to air pollution. For inclusion in the study, each subject was given a clinical medical history questionnaire in the presence of a doctor. The questions were about: age, sex, height and weight (to calculate body mass index: BMI), medical history with particular reference to cigarette smoking, occupational history, drug use, close and remote family medical history, and information about any non-occupational exposure to nickel (such as solvents, paints and pesticides). None of the subjects included in the study reported use of drugs or non-occupational exposure to Ni.

To avoid the influence of confounding factors, we excluded from the initial sample 11 diabetic subjects (67), for a total of 338 subjects. As to the cigarette smoking habit, they were classified according to the World Health Organization (WHO) into: smokers (subjects who reported smoking or having smoked at least 100 cigarettes in their lives, or having stopped smoking less than six months before); non-smokers (those who claimed not to smoke or to have smoked fewer than 100 cigarettes in their lives); and former smokers (those who claimed to have smoked at least 100 cigarettes in their lives, but had stopped smoking more than six months before).

The results that were below the LoD of the method of biological monitoring were expressed in values corresponding to the LoD divided by the square root of 2 (68). We subsequently excluded the subjects with values of biological monitoring below the LoD, that is 32 subjects for the urinary nickel, for a total of 306 subjects, and 248 subjects for serum nickel, having a total of 90 subjects. The evaluation was performed on both samples, the one including subjects with nickel values below the LOD (338) and the sample with subjects with nickel values only above the LoD.

The monitoring of Ni in blood and in urine was performed for each worker after four continuous working days at the end of the work shift. Each worker had been notified that they had to abstain from the consumption of certain foods (cocoa, chocolate, soya beans, oatmeal, walnuts and almonds, fresh and dried legumes) during the four days before the examination. A venous blood sample of 10 ml was taken from each worker. The blood samples were stored at the workplace in a refrigerator at +4°C until they were transferred, in a suitable container at the same temperature, to the laboratory where they were centrifuged and then stored at -20°C until they were analysed (within 3 days). The blood samples, after appropriate dilution, were analysed for the detection of the concentration of blood Ni through graphite furnace atomic absorption spectrometry. The detection limit of the method was equal to 5.0 mg/l for total blood Ni.

The urine samples were transported in a cooler at 4°C to the laboratory, and stored at -20°C until analysis. On all the samples of urine, the urinary creatinine was determined using the Jaffé method. Urine samples were examined by extraction with ammonium pyrrolidine dithiocarbamate (ADPC) and analysed by graphite furnace atomic absorption.

The Italian Society for the reference values for the general population proposed a reference value equal to 0.1-1.0 µg/l for serum nickel and 0.1-5.0 µg/l for urinary nickel (69).

The blood pressure measurement was performed with a mercury sphygmomanometer, in accordance with the guidelines of the WHO (70), in the morning between 8.00 am and 10.00 am. Three blood pressure measurements were carried out: the first one five minutes after taking the supine position, the second three minutes after the first one and the third, three minutes after the second one, without postural changes. The average of the three measurements was used to identify hypertensive basal subjects according to the classification ESC/ESH 2007 where hypertensive individuals have values of systolic BP [SBP] > 140 mmHg and/or diastolic blood pressure [DBP] > 90 mmHg.

To evaluate the variation in blood pressure due to postural change, and the differential blood pressure (difference of systolic and diastolic blood pressure passing from the supine position to the standing position), we measured blood pressure one minute after taking standing position, in accordance with the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (71).

The Pearson correlation coefficient was applied to assess the relationship between Ni and systolic and diastolic BP in supine and in standing positions, and the differential systolic and diastolic BP. Multiple linear regression analysis was performed considering the systolic and diastolic BP in supine and in standing positions, with the differential systolic and diastolic blood pressure as dependent variables and age and BMI as independent variables. The sample was divided for smoking habit and age. Having checked the distribution using the Kolmogorov-Smirnov test, and having detected a non-normal distribution, the values were transformed into logarithmic form.

Statistical analysis was performed using the software SPSS® Advanced Statistical™ 10.0 (SPSS Science, Chicago, IL).

## Results

In the sample of smokers, multiple linear regression analysis found a significant negative relationship between systolic blood pressure in the standing position and nickel blood (r =-0.181, p=0.041) (Tab. 1A). Multiple linear regression analysis also showed, in the sample of non-smokers, a significant negative relationship between systolic differential blood pressure and urinary nickel (R=-0.299, p=0.042) (Tab. 1B).

We divided the sample by age: class 1 (under the age of 30 years), class 2 (age between 30 and 50 years) and class 3 (age over 50 years), considering first of all the total sample, then dividing classes further by smoking habits.
In the total sample, the values of systolic and diastolic BP in the supine position are negatively correlated with blood nickel in individuals from class 3 (respectively r=-0.228, p=0.044 and r=-0.261, p=0.026) (Tab. 2A), while the urinary nickel always shows a statistically significant correlation with systolic differential blood pressure in class 3 (r =-0.377, p=0.044) (Tab. 2B). The linear regression confirms, in class 3, the correlation between blood nickel and systolic and diastolic BP in the supine position (respectively R=0.346, p=0.004 and R=-0.260, p=0.044) (Tab. 2A). It also shows, again in class 3, a relationship between blood nickel and systolic and diastolic BP in the standing position (respectively R=-0.376, p=0.002 and R=0.299, p=0.018) (Tab. 2A), and a relationship between urinary nickel and diastolic differential blood pressure (R=-0.519, p=0.021) (Tab. 2B).
For smokers in class 3, we found a statistically significant correlation between the values of blood nickel and supine systolic BP (r=-0.391, p=0.030), and systolic and diastolic BP in the standing position (respectively r =-0.468, p=0.007 and r=-0.355, p=0.046), and a positive correlation between the values of blood nickel and diastolic differential BP (r=0.717, p=0.030) (Tab. 2C).
The linear regression confirms, in smokers of class 3, the statistically significant correlation between the values of blood nickel and in supine systolic BP (R=-0.428, p=0.016), and systolic and diastolic BP in the standing position (respectively R=-0.481, p=0.006 and R=-0.370, p=0.048) (Tab. 2C). It also shows, in non-smokers of class 2, a negative relationship between urinary nickel and systolic differential blood pressure (R=-0.405, p=0.015) (Tab. 2D).
After excluding subjects with blood and urinary nickel values below the LOD, the significances in the non-smokers sample were not confirmed.

## Discussion

Hypertension is the most important risk factor for cardiovascular disease. It was estimated that hypertension causes about 7.5 million deaths a year worldwide, accounting for 12.8% of all causes of death (72).
Outdoor workers are exposed to numerous urban pollutants, including various metals present in urban air, coming both from the exhaust fumes of the factories, and from domestic and vehicular emissions. Biological monitoring is a valuable instrument for the assessment

**Table 1 A - Serum nickel: statistical correlation and multiple linear regression analysis for non smokers sample and smokers sample.**

| Variables | | B.P. | Correlation | Serum nickel | Multiple linear regression | Serum nickel |
|---|---|---|---|---|---|---|
| | **Supine position** | max | r | .050 | R | .067 |
| | | min | P | .533 | P | .360 |
| | | | r | .011 | R | .069 |
| | | | P | .889 | P | .330 |
| **Non smokers sample** | **Standing position** | max | r | .077 | R | .094 |
| | | | P | .345 | P | .201 |
| | | min | r | .042 | R | .082 |
| | | | P | .609 | P | .259 |
| | **Differential pressure** | max | r | .173 | R | .246 |
| | | | P | .199 | P | .092 |
| | | min | r | -.097 | R | -.127 |
| | | | P | .530 | P | .437 |
| | **Supine position** | max | r | -.045 | R | -.120 |
| | | | P | .655 | P | .184 |
| | | min | r | -.069 | R | -.156 |
| | | | P | .487 | P | .098 |
| **Smokers sample** | **Standing position** | max | r | -.093 | R | **-.181** |
| | | | P | .346 | P | **.041** |
| | | min | r | -.049 | R | -.137 |
| | | | P | .618 | P | .148 |
| | **Differential pressure** | max | r | -.094 | R | -.073 |
| | | | P | .525 | P | .638 |
| | | min | r | .036 | R | -.086 |
| | | | P | .847 | P | .673 |

*B.P. = blood pressure*

of occupational exposure to chemicals. Both blood and urinary nickel represent good markers for exposure to nickel: blood Ni is considered an indicator of recent exposure to Ni because of its short half-life in the bloodstream. Wu et al. (73) found that blood concentrations of several metals that PM is composed of, including nickel, zinc, magnesium, strontium and arsenic, are correlated with systolic and diastolic blood pressure. The relationship between these transition metals and the blood pressure was demonstrated in studies *in vi-*

**Table 1 B - Urinary nickel: statistical correlation and multiple linear regression analysis for non smokers sample and smokers sample.**

| Variables | | B.P. | Correlation | Urinary nickel | Multiple linear regression | Urinary nickel |
|---|---|---|---|---|---|---|
| Non smokers sample | Supine position | max | r | -.014 | R | .018 |
| | | | P | .856 | P | .806 |
| | | min | r | -.121 | R | -.070 |
| | | | P | .126 | P | .331 |
| | Standing position | max | r | -.008 | R | .004 |
| | | | P | .924 | P | .959 |
| | | min | r | -.114 | R | -.081 |
| | | | P | .152 | P | .270 |
| | Differential pressure | max | r | -.238 | R | **-.299** |
| | | | P | .060 | P | **.042** |
| | | min | r | .091 | R | .150 |
| | | | P | .542 | P | .375 |
| Smokers sample | Supine position | max | r | -.004 | R | .027 |
| | | | P | .968 | P | .765 |
| | | min | r | .082 | R | .130 |
| | | | P | .409 | P | .166 |
| | Standing position | max | r | .062 | R | .110 |
| | | | P | .532 | P | .209 |
| | | min | r | .032 | R | .082 |
| | | | P | .744 | P | .383 |
| | Differential pressure | max | r | -.028 | R | .048 |
| | | | P | .848 | P | .758 |
| | | min | r | .053 | R | .030 |
| | | | P | .777 | P | .882 |

*B.P. = blood pressure*

**Table 2 A-D - Correlation and multiple linear regression between blood pressure and nickel in classes divided for age.**

**2A: Classes divided for age: serum nickel.**

| Serum nickel | | | correlation Classes divided for age Serum nickel | | | Multiple linear regression Classes divided for age Serum nickel | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1(<30) | 2(30-50) | 3(>50) | 1(<30) | 2(30-50) | 3(>50) |
| Supine position | max | r | .507 | .081 | **-.228** | .444 | .046 | **-.346** |
| | | p | .135 | .220 | **.044** | .329 | .513 | **.004** |
| | min | r | .548 | .025 | -.130 | .340 | -.010 | **-.260** |
| | | p | .101 | .709 | .252 | .337 | .891 | **.044** |
| Standing position | max | r | .551 | .107 | **-.261** | .487 | .077 | **-.376** |
| | | p | .098 | .109 | **.026** | .254 | .256 | **.002** |
| | min | r | .403 | .070 | -.192 | .241 | .044 | **-.299** |
| | | p | .249 | .299 | .104 | .479 | .528 | **.018** |
| Differential pressure | max | r | -.250 | .099 | -.276 | - | .073 | -.227 |
| | | p | .750 | .339 | .140 | - | .513 | .237 |
| | min | r | .333 | -.169 | .113 | - | -.253 | .356 |
| | | p | .667 | .169 | .644 | - | .058 | .096 |

**2B: Classes divided for age: urinary nickel.**

| Urinary nickel | | | correlation Classes divided for age Urinary nickel | | | Multiple linear regression Classes divided for age Urinary nickel | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1(<30) | 2(30-50) | 3(>50) | 1(<30) | 2(30-50) | 3(>50) |
| **Supine position** | max | r | -.002 | -.033 | .057 | .229 | .005 | .024 |
| | | p | .995 | .612 | .615 | .677 | .944 | .838 |
| | min | r | -.154 | -.025 | .000 | .330 | -.002 | -.007 |
| | | p | .650 | .705 | .998 | .450 | .974 | .955 |
| **Standing position** | max | r | .110 | -.029 | .089 | .444 | .013 | .038 |
| | | p | .747 | .664 | .456 | .393 | .845 | .744 |
| | min | r | .150 | -.069 | -.004 | .654 | -.043 | -.015 |
| | | p | .659 | .297 | .972 | .160 | .533 | .902 |
| **Differential pressure** | max | r | .366 | .003 | **-.377** | - | .038 | -.243 |
| | | p | .544 | .972 | **.044** | - | .736 | .235 |
| | min | r | .541 | .116 | -.189 | - | .177 | **-.519** |
| | | p | .347 | .337 | .452 | - | .186 | **.021** |

**2C : Classes divided for age divided for smoke: serum nickel.**

| Non smokers | | | correlation Classes divided for age Serum nickel | | | Multiple linear regression Classes divided for age Serum nickel | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1(<30) | 2(30-50) | 3(>50) | 1(<30) | 2(30-50) | 3(>50) |
| **Supine position** | max | r | .571 | .149 | -.213 | .590 | .104 | -.251 |
| | | p | .139 | .099 | .330 | .305 | .254 | .264 |
| | min | r | .563 | .073 | -.144 | .462 | .268 | -.046 |
| | | p | .146 | .420 | .513 | .317 | .416 | .842 |
| **Standing position** | max | r | .608 | .156 | -.155 | .635 | .128 | -.184 |
| | | p | .110 | .087 | .490 | .231 | .157 | .432 |
| | min | r | .431 | .100 | -.103 | .336 | .100 | -.020 |
| | | p | .286 | .273 | .648 | .358 | .269 | .928 |
| **Differential pressure** | max | r | -.250 | .177 | .632 | - | .290 | 2.431 |
| | | p | .750 | .234 | .178 | - | .069 | .366 |
| | min | r | .500 | -.132 | - | - | -.142 | - |
| | | p | .667 | .431 | - | - | .431 | - |
| **Smokers** | | | **1(<30)** | **2(30-50)** | **3(>50)** | **1(<30)** | **2(30-50)** | **3(>50)** |
| **Supine position** | max | r | - | .108 | **-.391** | - | .052 | **-.428** |
| | | p | - | .378 | **.030** | - | .873 | **.016** |
| | min | r | - | -.007 | -.324 | - | -.151 | -.343 |
| | | p | - | .952 | .075 | - | .249 | .072 |
| **Standing position** | max | r | - | .043 | **-.468** | - | -.071 | **-.481** |
| | | p | - | .727 | **.007** | - | .549 | **.006** |
| | min | r | - | .041 | **-.355** | - | -.098 | **-.370** |
| | | p | - | .737 | **.046** | - | .442 | **.048** |
| **Differential pressure** | max | r | - | .133 | -.525 | - | .121 | -.475 |
| | | p | - | .453 | .054 | - | .542 | .162 |
| | min | r | - | -.102 | **.717** | - | -.210 | .451 |
| | | p | - | .651 | **.030** | - | .601 | .151 |

*vo* (74). Once they reach the airways, these metals stimulate the production of reactive oxygen species and induce inflammation and tissue damage, resulting in cardiopulmonary response and vascular damage (75). In fact in our study, the correlations with blood nickel, an immediate marker responsible for inflammation, were detected in smokers, where it exacerbates the inflammatory effects of cigarette smoking. Urinary

**2D : Classes divided for age divided for smoke: urinary nickel.**

| Non smokers | | | correlation Classes divided for age Urinary nickel | | | Multiple linear regression Classes divided for age Urinary nickel | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1(<30) | 2(30-50) | 3(>50) | 1(<30) | 2(30-50) | 3(>50) |
| **Supine position** | max | r | -.055 | .010 | -.023 | -.115 | .052 | .026 |
| | | p | .896 | .913 | .915 | .846 | .576 | .904 |
| | min | r | -.045 | -.112 | -.281 | .107 | -.046 | -.164 |
| | | p | .916 | .205 | .193 | .824 | .611 | .478 |
| **Standing position** | max | r | .324 | -.004 | -.027 | .258 | .022 | -.011 |
| | | p | .433 | .966 | .904 | .631 | .810 | .962 |
| | min | r | .323 | -.137 | -.239 | .447 | -.105 | -.112 |
| | | p | .435 | .122 | .285 | .296 | .251 | .615 |
| **Differential pressure** | max | r | .660 | -.306 | -.111 | - | **-.405** | 2.043 |
| | | p | .340 | .026 | .834 | - | **.015** | .627 |
| | min | r | .762 | .096 | - | - | .137 | - |
| | | p | .448 | .550 | - | - | .452 | - |
| **Smokers** | | | **1(<30)** | **2(30-50)** | **3(>50)** | **1(<30)** | **2(30-50)** | **3(>50)** |
| **Supine position** | max | r | - | -.027 | .063 | - | -.031 | .044 |
| | | p | - | .825 | .732 | - | .797 | .788 |
| | min | r | - | .135 | .123 | - | .148 | .095 |
| | | p | - | .267 | .503 | - | .251 | .605 |
| **Standing position** | max | r | - | .054 | .132 | - | .094 | .568 |
| | | p | - | .658 | .464 | - | .423 | .575 |
| | min | r | - | .057 | .077 | - | .071 | .043 |
| | | p | - | .639 | .671 | - | .570 | .809 |
| **Differential pressure** | max | r | - | .199 | -.380 | - | .211 | -.328 |
| | | p | - | .266 | .162 | - | .285 | .293 |
| | min | r | - | .114 | -.422 | - | .151 | -.445 |
| | | p | - | .624 | .258 | - | .590 | .142 |

nickel markers of exposure showed significant correlations with the differential pressure in non-smokers, a sign of long-term effects resulting from prolonged exposure to low doses, and due to the metabolism of the metal, which in addition to carrying out the more immediate inflammatory processes, has time to interfere with the metabolism.

Our study revealed a relationship between systolic blood pressure in the standing position and blood nickel which is confirmed, stratifying by age, in older individuals and in individuals with longer work seniority, who show a relationship with the systolic and diastolic blood pressure both in the supine and in standing position. This would lead to the conclusion that the effects extend as that exposure is prolonged. As there are variations in systolic and diastolic blood pressure, there is no change in differential blood pressure. Urinary Ni is considered an index of prolonged exposure (76, 77) although others consider it an indicator of recent exposure (78). In our study it tends to maintain, despite the stratification by age, a correlation with differential blood pressure due to an increase, although not significant, of systolic blood pressure in the supine position in non-smoker subjects. Our results are confirmed by recent studies in the literature: Jacobs et al. (79) found that nickel is correlated with hypertension and pulse pressure in hypertensive patients receiving therapy, which confirms the results we have obtained in class 3. These effects on BP in the standing position and on the hormonal parameters, as demonstrated by our ongoing studies, may have an effect on the safety for some categories of exposed workers, effects which deserve further investigation with targeted studies.

Lind et al. (80) conducted a study on 1016 patients aged seventy, measuring the prevalence of carotid plaques, and then correlating it with blood concentrations of eleven metals (Al, Cd, Co, Cu, Cr, Hg Mn, Mo, Ni, Pb, and Zn). The levels of blood Ni correlated with the number of carotid arteries affected by plaque as a result of multiple regression analysis, after adjusting for the influence of variables such as sex, waist circumference, BMI, glycemic stick, blood pressure, HDL, LDL, triglycerides, smoking habits and intake of antihypertensive medications and statins. Other studies have reported elevated levels of Ni in the tissues and blood of patients suffering from coronary artery disease (81, 82). Lind et al. (83) have found a high concentration of copper and nickel in individuals suffering from left ventricular hypertrophy, especially the concentric type. Ni seems to affect the passage of current in the myocytes Ca channels of the T-type, influencing the mechanism of excitation and contraction of myocardium (84, 85).

These mechanisms appear to have an implication in the development of left ventricular hypertrophy (86).
The mechanism by which nickel would favour the deposit of plaque and the resulting arteriosclerosis, even after inhalation of low doses, may be explained by the fact that it is able to induce inflammation in the vascular wall, with consequent oxidative damage and plaque formation (87). This would also explain the damage to blood pressure in particular on individuals in class 3, aged over 50 years, so not only are they more exposed to Ni, but also predisposed to alterations of the vascular wall.
However, excluding individuals with blood and urinary nickel values below the LOD, the results in the sample of non-smokers were not confirmed.

## Conclusions

In relation to the above, the overall results of our study can not prove that the exposure to nickel has a real effect on blood pressure, although some partial results suggest further studies are necessary.

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