Association Between Metabolic and Hormonal Derangements and Professional Exposure to Urban Pollution in a High Intensity Traffic Area

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Rationale: Studies suggest a relation between exposure to air particulate matter $(PM)_{2.5}$ pollution and greater cardiovascular morbidity, as well as increased risk for obesity and diabetes. We aimed to identify association(s) between nutritional and metabolic status and exposure to environmental pollution in a cohort of policemen exposed to high levels of air pollution.

Methods: We considered adult municipal policemen, working in an urban area at high-traffic density with documented high levels of air $PM_{2.5}$ (exposed group) compared to non-exposed policemen. Clinical characteristics, including the presence/absence of metabolic syndrome, were recorded, and serum biomarkers, including adiponectin, leptin, and ghrelin, were assessed.

Results: One hundred ninety-nine participants were enrolled, 100 in the exposed group and 99 in the non-exposed group. Metabolic syndrome was documented in 32% of exposed group and in 52.5% of non-exposed group ($P = 0.008$). In the exposed group, we found a positive correlation between body mass index and serum leptin as well as in the non-exposed group ($P < 0.0001$). Within the exposed group, subjects with metabolic syndrome showed lower serum adiponectin ($P < 0.0001$) and higher leptin ($P = 0.002$) levels with respect to those without metabolic syndrome, whereas in the non-exposed group, subjects with metabolic syndrome showed only higher leptin levels when compared to those without metabolic syndrome ($P = 0.01$). Among the participants with metabolic syndrome, we found lower adiponectin levels in those of the exposed group with respect to the non-exposed ones ($P = 0.007$). When comparing the exposed and non-exposed groups, after stratifying participants for Homeostatic Model Assessment for Insulin Resistance >2.5, we found lower adiponectin levels in those of the exposed group with respect to the non-exposed ones ($P = 0.038$).

Conclusions: Exposure to air PM pollution was associated with lower levels of adiponectin in adult males with metabolic syndrome.

INTRODUCTION

In industrialized countries, air pollution determines risks for human health [1]. Particulate and gaseous emissions from motor vehicles contribute to increase the air pollution [2]. Diesel exhaust particles (DEPs), a category of particulate matter (PM) derived from diesel fossil fuels and combustible engines, are among the most abundant components of airborne PM with an aerodynamic diameter $<2.5 \mu m$ ($PM_{2.5}$) [1] and are considered major contributors to traffic-related PM in urban areas [2, 3]. The most part of DEP is composed by particles of nano-sized dimension [4], which are small aggregates of carbonaceous particles ($<100 nm$), representing a severe problem for human health considering that they remain in the atmosphere for long periods and go beyond to the indoor air environment, and they can be breathed determining a more toxic effect deeply into the lungs with respect to the coarse particles [5].

Particulate pollution is a major public health concern. Several epidemiological studies demonstrated that exposure to DEP is related to various cardiopulmonary, vascular, and oncologic diseases [6–9]. Moreover, carbonaceous nanoparticles derived from diesel engine exhaust are classified as human carcinogens [10, 11]. Recent data from large cohorts of subjects have shown strong associations between exposure to air $PM_{2.5}$ pollution and increased cardiovascular morbidity and mortality [12, 13]. Long-term air pollution exposure to fine $PM_{2.5}$ above US Environmental Protection Agency–defined standards has been reported to be associated with higher risk of neurodegenerative diseases, including Alzheimer disease [14].

Moreover, it has been reported that exposure to diesel exhaust PM may increase the risk for obesity and diabetes [15–17]. Recently, it has been demonstrated that an early exposure to high levels of $PM_{2.5}$ during life represents a risk factor for development of adiposity and insulin resistance in the subsequent years, likely mediated at least in part by reactive oxygen species generation [16]. Exposure for a long period of time to ultrafine particles in areas near highways has been associated with stroke, ischemic heart disease, hypertension, and type 2 diabetes [17, 18]. Robust data highlighted the association between long-term exposure to air pollution and type 2 diabetes and neurodegenerative disorders in adults, such as dementia and a general decline in cognition [19]. Another recent study identified the alteration of several metabolic pathways that mediate the development of asthma and cardiovascular diseases associated with ambient air pollutants [20]. Moreover, a study conducted in non-obese children exposed to high concentrations of $PM_{2.5}$, vs. low pollution controls, showed high circulating leptin and endothelin 1 levels, vitamin D deficiency, and food reward hormone dysregulation [21].

At present, few data are available on the association between hormone dysregulation, metabolic derangement, and chronic exposure to environmental contaminants.

By the present study, we aimed at identifying association(s) between nutritional, metabolic, and hormonal derangements and exposure to environmental pollution in an Italian population of traffic policemen professionally exposed to high levels of air $PM_{2.5}$ compared to employees performing indoor administrative work in the same area.

MATERIALS AND METHODS

This is a cross-sectional study performed on adult male municipal policemen of the city of Naples, Italy. The male gender was chosen because of the high percentage of male subjects working in this field in this specific geographical area.

This study was carried out in accordance with the health surveillance program (D.L. n.81/08), approved to be conducted at the Department of Public Health, University of Naples "Federico II," Italy. All the subjects gave written informed consent in accordance with the Declaration of Helsinki and authorized the use of the clinical data for research purposes. The privacy rights of human subjects were always observed. Exclusion criteria included the presence of highly catabolic diseases, such as cancer, chronic infections, and the absence of informed consent.

Participant Demographic and Clinical Characteristics

We enrolled adult males professionally exposed to air pollution (or airborne nanoparticles) in an urban area at high traffic density (exposed group) and adult males non-exposed (at least 1 year indoor working) (non-exposed group) matched by body mass index (BMI).

Demographic characteristics, including age, weight, height, BMI, and comorbidities, such as hypertension, diabetes, cardiovascular disorders, and dyslipidemia, were recorded in all participants. The diagnostic criteria we used for metabolic syndrome were based on the National Cholesterol Education Program Adult Treatment Panel III clinical criteria for defining the metabolic syndrome.

Biomarkers

Blood samples were collected in all the participants on fasting condition and then centrifuged, and the serum was stored at $-80°C$ at the Laboratory of the Department of Public Health, University of Naples "Federico II." The samples were shipped to the Central Laboratory for analysis at the Department of Translational and Precision Medicine (formerly Department of Clinical Medicine), Sapienza University of Rome. The glycemic–insulinemic profile,

including the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index and the complete lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), has been assessed by enzymatic and/or colorimetric methods.

The serum levels of leptin and adiponectin, as adipokines, and ghrelin, as gastrointestinal peptide, have been assessed by enzyme-linked immunosorbent assays.

We additionally utilized leptin/BMI and adiponectin/BMI ratios in our analyses accounting for the well-known associations between leptin and adiponectin with adiposity, as previously shown (22, 23).

Statistical Analyses

Participants' characteristics were described using mean ± SD for continuous normally distributed variables, median and interquartile range for non–normally distributed variables, as appropriate, and categorical variables were presented as number of cases (percentages). Skewed variables were transformed to the natural logarithm (LN). A Shapiro–Wilk test was used to determine normality. Relations among variables were assessed through χ^2 tests, t-tests, analysis of variance, or Wilcoxon rank-sum tests, as appropriate. Spearman correlation index was used for non-parametric correlations.

A standard two-tailed $P < 0.05$ was considered statistically significant. All statistical analysis was performed in SPSS®.

RESULTS

Characteristics of the Participants

A total of 200 participants were consecutively enrolled in the study during the second half of the year 2016: 100 adult males, who worked as traffic policemen exposed to airborne traffic–derived pollution in an urban area (Naples, Italy) at high traffic density (exposed group) (mean duration of the exposure was 20.2 years, min. 16, max. 29 years), and 100 adult males with administrative duties performed in the office in the same city (non-exposed group). One participant of the non-exposed group was excluded because he did not perform blood sampling and did not respond to the administered questionnaires. Therefore, 99 participants in the non-exposed group were studied.

According to the Air Quality Monitoring Report 2016 by the Regional Agency for Environmental Protection in Campania, Italy, during the 3 months before the enrollment, the traffic policemen were exposed to daily mean $PM_{2.5}$ values between 13.97 and 23.37 µg/m³. The same agency recommends maximum values of $PM_{2.5}$ of 25 µg/m³ during the entire year (http://www.arpacampania.it/home). No differences were observed between exposed and non-exposed groups in terms of cigarette smoking. In particular, the exposed group included 30 smokers (30%), and 21 of them (70%) smoking more than 10 cigarettes/day. Non-exposed group included 31 smokers (31.3%), and 27 of them (87%) smoking more than 10 cigarettes/day.

TABLE 1 | Participants' characteristics.

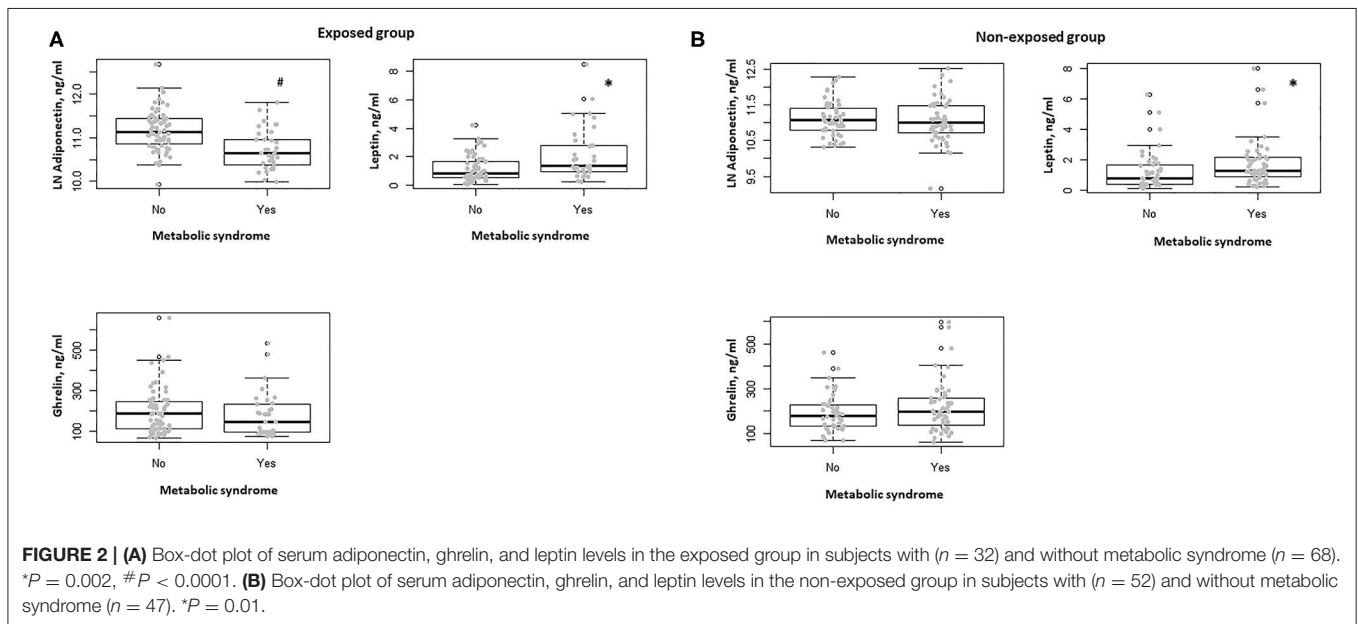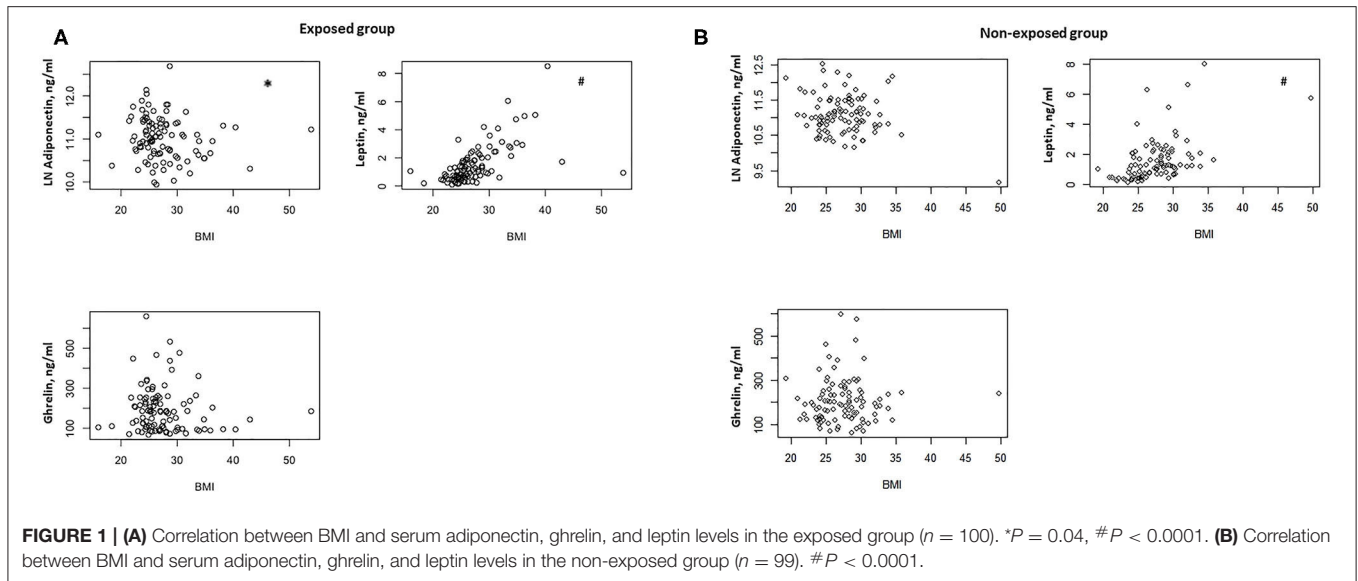|	Exposed group	Non-exposed group	P
	Participants $n = 100$	Participants $n = 99$	
Age, years	58.0 (47.75, 61.0)	61.0 (57.0, 63.0)	< 0.0001
Body weight, kg	80.0 (75.0, 90.0)	82.5 (75.0, 90.0)	0.52
BMI, kg/m²	26.2 (24.5, 28.7)	27.3 (24.9, 29.4)	0.28
BMI ≥30 kg/m², n (%)	22 (22%)	23 (23.2%)	0.84
Cholesterol, mg/dL	181.0 (160.8, 213.0)	185.0 (158.5, 209.5)	0.81
LDL cholesterol, mg/dL*	116.3 ± 37.1	114.8 ± 35.8	0.78
Triglycerides, mg/dL	116.5 (72.0, 151.8)	107.0 (85.0, 156.0)	0.93
Fasting glucose levels, mg/dL	96.5 (89.0, 106.3)	104.0 (92.0, 116.5)	0.009
Insulinemia, µU/mL	10.5 (6.45, 17.15)	12.5 (7.56, 18.4)	0.10
HOMA-IR index	2.39 (1.46, 4.08)	3.16 (1.81, 5.05)	0.03
Comorbidities, Yes/No:			
Hypertension	30/70	46/53	0.025
Diabetes mellitus	7/93	10/89	0.445
Dyslipidemia	34/66	28/71	0.38
Metabolic syndrome	32/68	52/47	0.008
LN adiponectin, ng/mL*	11.02 ± 0.5	11.09 ± 0.55	0.39
LN ghrelin, ng/mL*	2.22 ± 0.23	2.26 ± 0.20	0.13
Leptin, ng/mL	1.1 (0.63, 2.00)	1.14 (0.56, 1.99)	0.81

Median (interquartile range) is shown for non–normally distributed variables.
*Mean ± SD.
BMI, body mass index; LDL, low-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LN, natural logarithm.

Nutritional and Metabolic Profile of the Participants

No differences were observed between the two groups in terms of body weight, BMI, and lipid profile, whereas plasma glucose levels and HOMA-IR were higher in the non-exposed group compared to the exposed one ($P = 0.009$, $P = 0.03$, respectively) (**Table 1**). In addition, BMI was ≥30 kg/m² in 22% of the exposed group and in 23.2% of the non-exposed group (**Table 1**). The presence of comorbidities was as follows: diabetes was present in 7% in the exposed group and in 10.5% of the non-exposed group; hypertension was more frequent in the non-exposed group ($P = 0.025$); dyslipidemia was present in 45% of participants in the exposed group and 43.4% of the non-exposed ones (**Table 1**). Metabolic syndrome was documented in 32% of the exposed group and in the 52.5% of the non-exposed group ($P = 0.008$) (**Table 1**). Between the two groups, no differences were seen in terms of adiponectin, ghrelin, and leptin serum levels (**Table 1**), also when considering these values as ratio with BMI.

FIGURE 1 | (A) Correlation between BMI and serum adiponectin, ghrelin, and leptin levels in the exposed group ($n = 100$). *$P = 0.04$, #$P < 0.0001$. **(B)** Correlation between BMI and serum adiponectin, ghrelin, and leptin levels in the non-exposed group ($n = 99$). #$P < 0.0001$.

FIGURE 2 | (A) Box-dot plot of serum adiponectin, ghrelin, and leptin levels in the exposed group in subjects with ($n = 32$) and without metabolic syndrome ($n = 68$). *$P = 0.002$, #$P < 0.0001$. **(B)** Box-dot plot of serum adiponectin, ghrelin, and leptin levels in the non-exposed group in subjects with ($n = 52$) and without metabolic syndrome ($n = 47$). *$P = 0.01$.
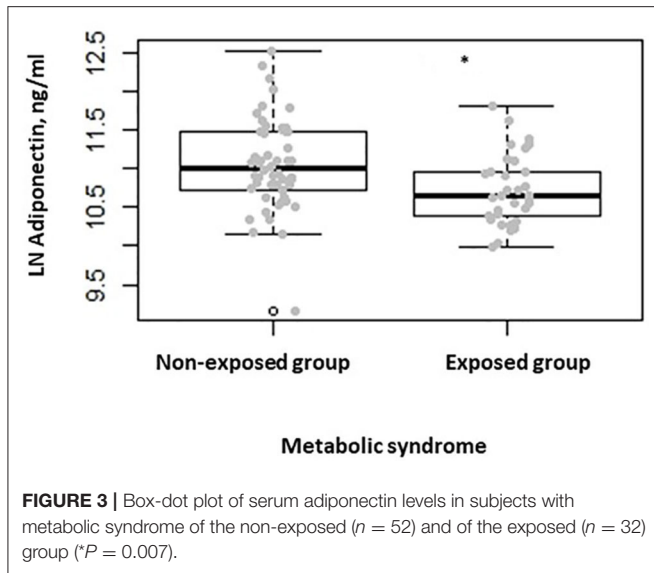
Correlation Between BMI and Serum Adiponectin, Ghrelin, and Leptin in the Two Groups of Participants

In the exposed group, we found a negative correlation between BMI and serum adiponectin levels ($\rho = -0.0205$, $P = 0.04$) (**Figure 1A**) and a positive correlation between BMI and serum leptin concentrations ($\rho = 0.667$, $P < 0.0001$) (**Figure 1A**). No significant correlation was documented between BMI and serum ghrelin levels (**Figure 1A**).

In the non-exposed group, we found a positive correlation between BMI and serum leptin ($\rho = 0.546$, $P < 0.0001$) (**Figure 1B**), but no significant correlations were detected between BMI and serum adiponectin and ghrelin (**Figure 1B**).

Association Between Comorbidities, Metabolic Syndrome, and Serum Adiponectin, Ghrelin, and Leptin Levels in the Two Groups of Participants

In the exposed group, participants with diabetes showed lower serum adiponectin levels with respect to non-diabetic ($P = 0.001$). No association was observed between the other comorbidities, including obesity, hypertension, dyslipidemia, and serum adiponectin, ghrelin, and leptin levels. Subjects in this group with metabolic syndrome showed lower serum adiponectin levels and higher serum leptin levels with respect to those without metabolic syndrome ($P < 0.0001$, $P = 0.002$, respectively) (**Figure 2A**). This observation was confirmed

FIGURE 3 | Box-dot plot of serum adiponectin levels in subjects with metabolic syndrome of the non-exposed ($n = 52$) and of the exposed ($n = 32$) group (*$P = 0.007$).

when correcting per BMI both serum levels of adiponectin (adiponectin/BMI) ($P < 0.0001$) and leptin (leptin/BMI) ($P = 0.003$).

In the non-exposed group, no differences in serum adiponectin, ghrelin, and leptin levels were documented between diabetic and non-diabetic participants and when considering the presence of obesity, hypertension, and dyslipidemia. In the non-exposed subjects with metabolic syndrome, we found no significant difference in terms of serum adiponectin levels, whereas higher serum leptin levels were observed when compared to those without metabolic syndrome ($P = 0.58$, $P = 0.01$, respectively) (**Figure 2B**). Also, in this group, this behavior was confirmed when correcting per BMI both serum levels of adiponectin (adiponectin/BMI) ($P < 0.0001$) and leptin (leptin/BMI) ($P = 0.018$).

Metabolic Syndrome and Metabolic Biomarkers Between the Two Groups of Participants

When comparing the two groups after stratifying participants for the presence of metabolic syndrome, we found lower serum adiponectin levels in the exposed group when compared to the non-exposed one ($P = 0.007$) (**Figure 3**). No differences were seen in terms of serum leptin, ghrelin, insulin, and fasting plasma glucose levels. Finally, when comparing the two groups, after stratifying participants for HOMA-IR > 2.5, as indicator of insulin resistance (24), we found lower adiponectin serum levels in the exposed group with respect to the non-exposed ($P = 0.038$).

DISCUSSION

A large number of studies performed worldwide have shown that environmental pollution due to exhaust particles and gas from diesel engine vehicles heavily impacts human health (1–3, 9, 10).

In the last 10 years, several scientific reports highlighted the dangerous effects for human health deriving from the exposure to DEP. The contact of micro (PM 10–2.5 μm) and/or nano (PM < 100 nm) sized particles with mucous membranes of the respiratory systems through breathing, the potential achievement of the brain tissue through nasal inhalation, and the direct absorption through the skin have been considered the main entrance doors of the particles into the human body. Several data both *in vitro* and *in vivo* have documented the deleterious effects of DEP. The impact on different cell systems has been assessed, as well as the underlying cellular mechanisms regulating the biological effects between pollution-derived particles (25–30). It has been widely demonstrated that the biological effects of urban traffic pollution are mediated by inflammatory mechanisms.

The results of our study, aimed at investigating the potential effects of environmental pollutants on metabolic and hormonal parameters in people exposed professionally to urban traffic, showed that, when comparing the two groups of participants (exposed vs. non-exposed), no differences were detectable in terms of serum adiponectin, ghrelin, and leptin levels. However, in the two groups we confirmed the presence of a positive correlation between BMI and leptin concentrations, as expected to be influenced by adiposity, while the negative correlation between BMI and adiponectin was present only in the exposed group, where also the presence of diabetes was associated with lower serum adiponectin levels. A similar behavior was shown regarding the association between metabolic syndrome and changes in terms of both adiponectin (lower) and leptin (higher) circulating levels only in the exposed group; in fact, in the non-exposed subjects, only leptin serum levels were higher in subjects with metabolic syndrome. More importantly, when comparing the two groups after stratifying participants for the presence of metabolic syndrome, as well as for HOMA-IR > 2.5 alone, we found significantly lower serum adiponectin levels in the exposed group with respect to the non-exposed. Among the metabolic and hormonal parameters (insulin, ghrelin, and leptin), our data suggest that the prolonged daily exposure to high levels of urban pollution, as documented by the report of the Regional Agency for Environmental Protection, significantly affected only the adiponectin serum levels.

Adiponectin is a 244-amino-acid protein, produced almost exclusively by white adipocyte cells, mostly by visceral depots (31); it possesses a wide range of biological activities, mainly including an insulin-sensitizing and antiatherogenic function, and has been identified as a potent and pleiotropic regulator of inflammation (32–35). Experimental studies have provided strong evidences that major cellular responses to PM exposure include oxidative stress and inflammation (36, 37). The majority of the effects induced by exhaust emissions determine the triggering of inflammatory responses in exposed individuals and the gradual release of cytokines, reactive oxygen species, nitric oxide synthase, and other defense mechanisms, which ultimately expose the DNA to negative oxidative effects (38). Moreover, several recent studies highlighted the fundamental role played by PM exposure in the pathogenesis of the metabolic syndrome and cardiovascular disorders (39). Increased $PM_{2.5}$ exposure has been shown to promote elevations in blood pressure among

healthy subjects and in particular among obese individuals who resulted more susceptible to the effects of ambient air pollution (40). High levels of air PM with diameter ≤ 10 and $2.5 \, \mu m$ have been demonstrated to impair myocardial perfusion and increase myocardial oxygen demand in non-smoking patients with metabolic syndrome (41). Air pollution has been implicated in the pathogenesis of metabolic syndrome associated with other metabolic disorders (42, 43).

A hormonal derangement, likely triggering the onset of the metabolic syndrome during prolonged exposure to PM_{10}, has been reported (44).

Our findings on reduced adiponectin serum levels in exposed subjects with metabolic syndrome are supported by a recent study reporting higher levels of cadherin 13 upon exposure to PM_{10} that, resulting in reduced levels of free adiponectin, could affect insulin resistance, as adiponectin is crucial to its reduction. The authors suggested that long-term exposure to PM_{10} may interfere with insulin metabolism, as adiponectin plays a central role in regulating insulin levels (45, 46).

A more recent study showed that exposure to 1-year average $PM_{2.5}$ is associated with an increased risk of metabolic syndrome and its components in adults without cardiovascular disease, thus indicating that $PM_{2.5}$ affects the onset of metabolic syndrome, which may lead to increase the risk of cardiovascular disease (47). A significant association of short- and long-term exposures to $PM_{2.5}$ with hypertension has been observed with a stronger relationship among studies of men from Asia, North America, and areas with higher air pollutant levels (48).

Regarding our study, we should consider that the city of Naples is on the seaside, exposed during almost all hours of the day to the sea breeze or wind. It is likely that these windy atmospheric conditions are able to disperse gaseous and particulate exhaust components decreasing considerably their inhaled portion, thus potentially reducing their dangerous effects. In this light, the metabolic derangements that we observed in a small percentage (32%) of our exposed group might be even worse in a more polluted metropolitan area.

Our study has limitations, including the absence of an objective assessment of physical activity/inactivity, in particular in the non-exposed group. However, we assume that the exposed group is more physically active that the non-exposed one at least during the working time.

We did not assess food intake, which might help in correlating metabolic and hormonal changes with energy and protein imbalance. To account for adiposity, we did not measure waist circumference, as well as body composition, although we corrected the levels of the biomarkers for body size (BMI).

We considered only male subjects, and more importantly, we are not able to ascertain the effect of a single subject's exposure to pollution and to cigarettes smoking, as potentially additive effects, and the change in hormonal and metabolic profile in a longitudinal fashion. Moreover, a higher percentage of hypertensive and metabolic syndrome individuals in the non-exposed cohort might have impacted on the correlations observed. However, considering that the exposed group is the one showing significantly higher metabolic dysregulations in terms of leptin and adiponectin levels, we believe that the data obtained within this group appear reliable, although a cause-effect investigation is needed to clarify these observations.

In conclusion, the significantly lower circulating adiponectin levels documented in the exposed group with metabolic syndrome appear clinically important, suggesting that the exposed group, despite protective factors such as non-sedentary daily activity, is subjected to undergo metabolic changes likely due to the observed reduced levels of the hormone adiponectin (which possesses a protective function against inflammation) potentially induced by environmental pollution. Based on these findings, it is possible to hypothesize that being constantly exposed to traffic-derived pollutants may induce metabolic derangements that could lead, if added to other risk factors, including genetic background and unbalanced dietary habits, to the development of chronic diseases including diabetes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AM designed research, analyzed data, and wrote the paper. MA collected the data and wrote the paper. MM and UC reviewed the paper. AG and RA conducted research and collected the data. CR performed laboratory dosage. AS performed statistical analyses. LC, GMa, AN, and GMu collected the data and reviewed the paper. MT conducted the research and reviewed the paper. SF designed research, wrote the paper, and had primary responsibility for final content. All authors contributed to the article and approved the submitted version.

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