

## Gender and cancer of respiratory system in old ages in four big Italian cities: air pollution effect?

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**Summary.** *Introduction.* Exposure to fine particulate matter air pollution is known to be an important risk factor for cancer of the respiratory system (CRS) although cigarette smoking is far more serious as an individual risk factor. High levels of average annual concentration of fine particulate matter are to be found in Italian cities, with Turin, Milan, Naples and Rome leading the list of Europe's largest cities.

*Methods.* In this study we compared — separately for the two genders — the CRS mortality rates of people aged 65 and over resident in the four mentioned Italian cities with the rates registered in both the surrounding areas of the corresponding provinces and Italy overall, for the mean of the years 2014 and 2015. We focused on deaths of elderly people, as the risk of death due to this cause involves a long period of exposure to the determining factors before it manifests itself.

*Results.* The separate analysis of the two genders showed that women resident in the four cities present CRS mortality rates that are substantially higher than in the rest of the provinces and in Italy overall. For men, by contrast, the territorial differences are limited and it is not always those living in the cities who are more penalised. Given the high levels of female mortality, the well-known disadvantage of men in the levels of mortality from this cause of death tends to decrease in the cities.

*Discussion.* It is known that female smoking has involved more recent cohorts, and, among those considered, women born after the 1940s, for whom smoking was a factor of emancipation among the more highly educated. Is it possible that the disadvantage of women in the cities, characterised by higher educational levels, is related to smoking habits alone and not to the harmful effects of environmental pollution in urban areas? Do the harmful effects of air pollution act differently on the two genders, penalizing women more? Based on the data used, we have no answers to these questions. Data for cohorts and more statistical information on environmental and individual risks in studies that give greater attention to gender differences might help to clarify some of the aspects identified here on the mortality of elderly women who are resident in Italy's most polluted areas.

**Key words.** Particulate matter air pollution, mortality from cancer of the respiratory system, gender differences, smoking habits, territorial differences.

**Genere e tumore dell'apparato respiratorio in età avanzata in quattro grandi città italiane: effetto 'mal'aria'?**

**Riassunto.** *Introduzione.* L'esposizione all'inquinamento atmosferico dovuto alla concentrazione di polveri sottili è stata riconosciuta come un importante fattore di rischio per il tumore maligno dell'apparato respiratorio, seppur di gravità non paragonabile rispetto al ben noto rischio a livello individuale legato al fumo di sigaretta. Alti livelli di concentrazione media annua di polveri sottili caratterizzano le città italiane, con Torino, Milano, Napoli e Roma ai primi posti in una graduatoria sul livello di inquinamento atmosferico nelle più grandi città europee.

*Metodi.* In questo studio abbiamo confrontato, distintamente per i due generi, i tassi di mortalità per tumore maligno dell'apparato respiratorio degli ultrasessantacinquenni residenti nelle quattro grandi città italiane con i tassi nelle circoscrizioni provinciali e con quello nazionale relativamente alla media degli anni 2014 e 2015. Lo studio è stato condotto sulla popolazione anziana poiché il rischio di morte per questa causa, per manifestarsi, ha bisogno di un lungo periodo di esposizione ai fattori che lo determinano.

*Risultati.* Dall'analisi distinta dei due generi, è emerso che le donne residenti nelle quattro città presentano tassi di mortalità per il tumore maligno dell'apparato respiratorio consistentemente più elevati rispetto alla restante area delle rispettive province e al livello nazionale. Per gli uomini, invece, si rilevano differenze territoriali contenute e non sempre i residenti nelle città risultano più penalizzati. Dati gli alti livelli di mortalità femminile, il ben noto svantaggio maschile nei livelli di mortalità per questa causa tende a ridursi nelle città.

*Discussione.* È noto che l'abitudine al fumo tra le donne ha coinvolto le coorti più recenti e, tra quelle considerate, le donne nate dopo gli anni Quaranta, per le quali ha rappresentato un fattore di emancipazione tra le più istruite. È possibile dunque che lo svantaggio delle donne nelle città, dove presentano più alti livelli di istruzione, sia da mettere in relazione soltanto con la differente abitudine al fumo e non anche con gli effetti nocivi dell'inquinamento atmosferico delle aree urbane? È inoltre possibile che gli effetti nocivi dell'inquinamento dell'aria agiscano in maniera differente nei due generi penalizzando maggiormente le donne? Ovviamente, sulla base dei dati utilizzati non siamo in grado di dare risposte ai quesiti posti. Dati per coorte, e maggiori informazioni statistiche sui rischi ambientali e individuali all'interno di studi che dedichino maggiore attenzio-

ne alle differenze di genere, sarebbero necessari per aiutare a chiarire alcuni degli aspetti qui evidenziati circa la mortalità delle donne anziane residenti nelle aree italiane più inquinate.

**Parole chiave.** Inquinamento atmosferico da polveri sottili, mortalità per cancro dell'apparato respiratorio, differenze di genere, abitudine al fumo, differenze territoriali.

## 1. Introduction

In a recent study published in the *Proceedings of the National Academy of Sciences*, 54 researchers considered air pollution a genuine planetary emergency<sup>1</sup>. While stating that the risk of falling ill and dying of pollution is becoming significant for individuals mainly in the most polluted areas – though cigarette smoking is far more serious as an individual risk factor – the study indicated a 120% increase in collectively avoidable deaths that can be attributed to air pollution, placing this risk factor as one of the most important for mortality from some causes of death in the world, slightly below those due to diet and decidedly higher than smoking. The study showed that the population exposed to pollution is distributed very unequally in the world. While in Canada, the United States and Oceania (exposure to ambient fine particulate matter - PM<sub>2.5</sub> of 8 µg/m<sup>3</sup>) the deaths attributable to pollution are approximately 230,000 a year, in Western Europe (average exposure of 13 µg/m<sup>3</sup>) total deaths are 440,000. In the most polluted parts of the world like China, India and the Middle East (with average exposures of 60 to 85 µg/m<sup>3</sup>) the victims amount to 5,000,000.

The most recent report of Legambiente on air pollution in Italian cities *Mal'Aria 2018* (*mal'aria* meaning 'bad air or air pollution') showed that Italy's exposure to air pollution is chronic, and since 2013 more than 60% of the Italian population resident in urban areas has been exposed to concentrations of particulate matter PM<sub>10</sub> above the daily limit allowed by law (50 µg/m<sup>3</sup>, not to be exceeded more than 35 days a year)<sup>2</sup>. Compared with the European average, which is around 16.3%, the percentage of those exposed in Italy is decidedly too high. The Legambiente report also noted that "the large Italian cities are some of the most critical for atmospheric pollution: the worst values regarding the average annual concentration of fine particulate matter (PM<sub>10</sub>) are registered in Italy, with Turin (39 micrograms/cubic metres µg/m<sup>3</sup> of PM<sub>10</sub>), Milan (37 µg/m<sup>3</sup>) and Naples (35 µg/m<sup>3</sup>), which far exceed their European counterparts such as Seville, Marseilles and Nice, where there is an average annual concentration of PM<sub>10</sub> of 29 µg/m<sup>3</sup>. Rome and Paris are in seventh position, with an annual average concentration of 28 µg/m<sup>3</sup>".

Italy has already been subjected to two procedures for breaching regulations by the European Commission as a result of exceeding the thresholds of both PM<sub>10</sub> and nitric oxide (NO<sub>2</sub>), which is also a serious health risk. Most of the NO<sub>2</sub> emissions come from road traffic, and in particular from diesel engines.

Numerous Italian epidemiological studies<sup>3-8</sup> and the most recent research by the WHO on the relations between mortality and exposure to environmental pollution<sup>9</sup>, as well as Legambiente's latest report<sup>2</sup>, suggest that we should explore the risk of death from one of the main causes of cancer of the respiratory system (hereinafter CRS) in the four main Italian cities named in the report *Mal'aria 2018*, i.e., Turin, Milan, Rome and Naples. Bearing in mind that *mal'aria* can also indirectly indicate *male d'aria* – that is, illness caused by air pollution, created by poisonous emissions from excessive traffic in large cities – the aim of this work is to see whether mortality from CRS in the indicated cities is higher than in other neighbouring areas or in Italy overall.

Why CRS? It is well known that atmospheric pollution is also a risk factor for other illnesses, such as cardiovascular diseases – including ischaemic heart diseases and strokes –, chronic obstructive pulmonary diseases, respiratory infections<sup>6,7,9,10-15</sup> and female breast cancer (the risk of death linked to breast cancer increased by 80% every 10 µg/m<sup>3</sup> increase in exposure to PM<sub>2.5</sub>)<sup>16</sup>. For CRS – more than 90% of which is concentrated in the lungs – atmospheric pollution is a particularly important risk factor. Obviously, for this kind of cancer, which is closely correlated with cigarette smoke, atmospheric pollution is a risk factor that plays a leading role on its own and in combination with active/passive smoking. Many studies have revealed these relations, starting from follow-up enquiries conducted on cohorts of individuals resident in large cities<sup>17,18</sup>. Cesaroni et al. in a recent study of about 1,300,000 subjects aged 30 years and over, who had been living in Rome for at least 5 years at baseline, showed there was strong evidence of an association between lung cancer mortality and both NO<sub>2</sub> and PM<sub>2.5</sub> in 9 years of follow-up between 2001 and 2010<sup>7</sup>. Similar results emerged from another recent Italian study which analysed more than 400,000 deaths among residents aged 35 years and over in 25 cities in the period 2006-2010<sup>8</sup>. Significant effects were measured both for NO<sub>2</sub> and PM<sub>2.5</sub> on mortality from diseases of the respiratory system, though with some local differences due to the probable presence of factors specific to each city.

Our research analysed women and men over the age of 65, as the risk of death from this cause needs a long period of exposure to the determining factors before it manifests itself. It is therefore in old age that it expresses its full potential. Even when cancer is present at earlier ages, treatment often succeeds in postponing death

until more advanced ages. We believe that the gender comparison is particularly important as, though mortality for CRS (especially for lung cancer) has been and is still more common in men, the magnitude of the difference between the two genders continues to decline due to increases in the female mortality rates against a decrease among men<sup>19</sup>.

Clearly, a cross-sectional work like this on the whole population of the areas under consideration will not establish any cause-effect relationship between the main risk factors and mortality from cancer. That is why the title is worded as a question to which it is difficult to give clear and certain answers. In any case, the aim was simply to see whether mortality from CRS is higher in the 4 major cities – indicated as among the leading cities in Europe for levels of PM<sub>10</sub> – than in the rest of the surrounding towns in the same province, and also, obviously, than the Italian average. Particular attention was given to the mortality of women aged over 65, including both the cohorts born after the 1940s, who were among the first to take up cigarette smoking (65-74 years), and older (75 years and over), who were less exposed to the habit, while air pollution certainly affected both cohorts in the metropolitan cities considered in this study.

## 2. Data and methods

We used data from the Italian National Vital Statistics Death Registry, which is managed by the Italian National Institute of Statistics (Istat).

Focusing on deaths due to CRS, we considered the group of 'malignant neoplasms of respiratory and intrathoracic organs' (codes C30-C39 of the International Classification of Diseases, 10<sup>th</sup> Revision) in the years 2014 and 2015. We compared the mortality rates for both genders for the selected group of causes observed among people aged 65 and over who were resident in the cities of Turin, Milan, Rome and Naples, both with the rates registered in their respective provinces (excluding the area of the cities) and with the national rate. We preferred not to limit our study to lung cancer alone in order to have more extensive data and hence a more comprehensive statistical completeness.

For each geographical area of interest and each of the two genders, we calculated mortality rates for five-year age groups and standardised mortality rates, for the mean of the years 2014 and 2015. Standardisation was carried out using the resident population in Italy on 1 January 2015 as the standard population.

Percentage variations in mortality rates enabled us to measure, separately for men and women, the differentials in CRS mortality rate between the four cities and the remaining areas of the corresponding provinces, as well as Italy.

## 3. Results

### Women

Table 1 shows the standardised mortality rates for CRS by gender and area of residence. Among women aged over 65 years, the mortality rates in the four cities were higher than those registered in both the rest of the corresponding provinces and Italy. Percentage variations in mortality rates between cities and the rest of the provinces are consistent, varying between 28% of Turin and 49% of Naples (Figure 1). Compared with the national level, rates in the cities were up to 70% higher, and the maximum differential was observed for women resident in Rome.

Restricting the analysis to the oldest cohorts in the study represented by the '85 years and over' age group, the results were confirmed for all cities except Turin, where mortality for CRS was higher in the rest of the province (Table 1).

Interestingly, considering total mortality, its levels in all the main cities and for all ages (Table 1) were always, unlike what was observed for CRS mortality, lower than the values registered elsewhere in the provinces.

Table 2 shows mortality rates by 5-year age groups between 65-69 years and 80-84 years, excluding therefore the age groups over 84 years, which showed more volatile values in the rates. In all age groups, mortality rates among female residents in the four cities exceeded those observed in both the rest of their corresponding provinces and Italy. Percentage variations were generally high in all age groups (Figures 2 and 3). Special attention should be paid to women resident in Naples, where the variations with the rest of the province increased with age, reaching the value of 70% among people aged 80-84 years old (Figure 2). Compared with the national level, women resident in Rome presented mortality rates more than 60% higher in all age groups, reaching almost 80% in the 75-79 years age group (Figure 3).

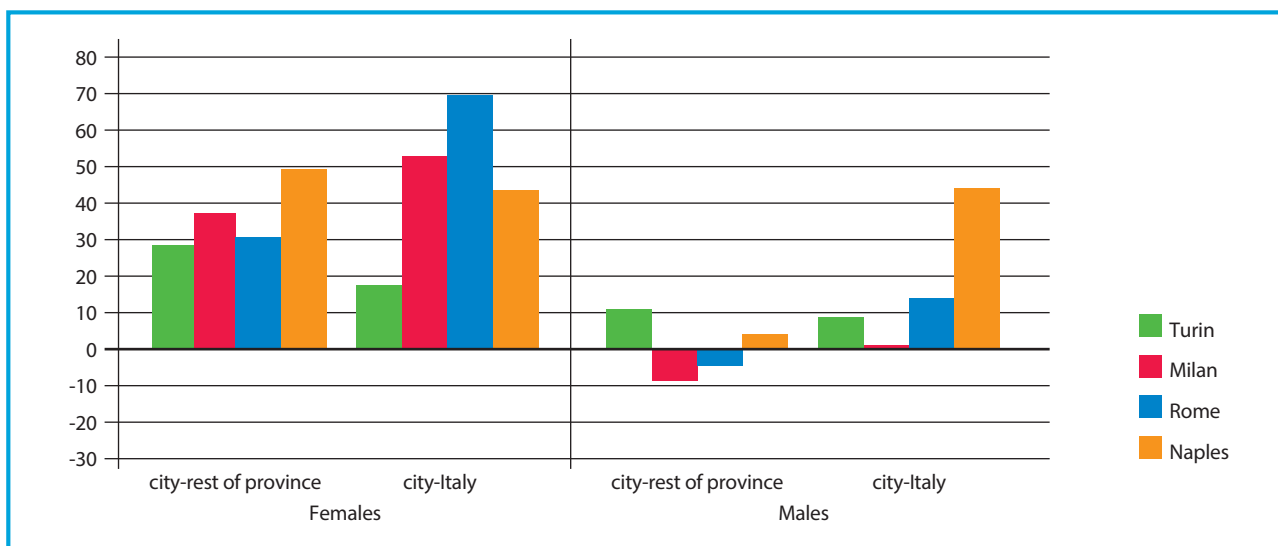
### Men

Among men, residents over 65 years of age in the cities of Turin and Naples present levels of mortality for malignant neoplasms of the respiratory system higher than those registered in the rest of the corresponding provinces and at national level. In the cities of Milan and Rome, the mortality rates for this group of causes were higher than that observed for Italy but lower than in the rest of the provinces (Table 1). Percentage variations were, however, generally moderate, with the exception of Naples, where the mortality rate was 44% higher than the national level (Figure 1), and this disadvantage was confirmed in all the 5-year age groups with a maximum distance of about 80% at 70-74 years (Figure 3).

Considering overall mortality, the figures for men also confirmed higher values in the rest of the prov-

**Table 1.** Standardised mortality rates (per 10,000) for malignant neoplasms of respiratory and intrathoracic organs (CRS), and total mortality, by gender and area of residence. Deaths at age 65 and over and 85 and over, and gender gap in mortality rates. Years 2014-2015.

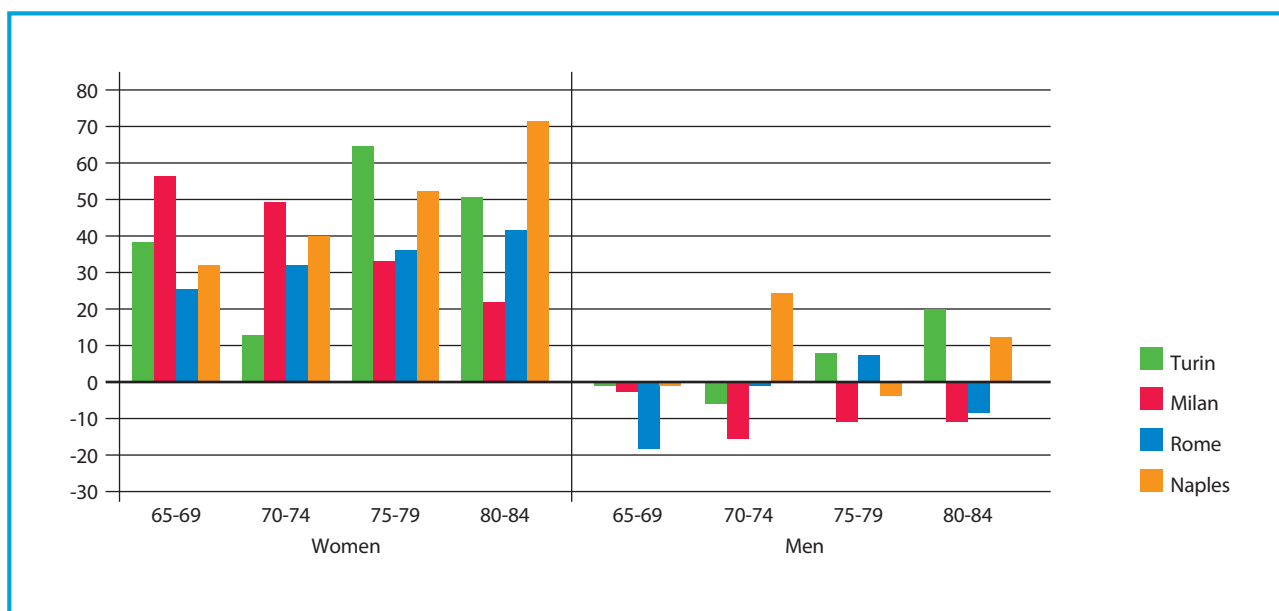
Area of residence		Women		Men		Gender gap (W/M)	
		65 years and over (a)	85 years and over (b)	65 years and over (c)	85 years and over (d)	65 years and over (c/a)	85 years and over (d/b)
<i>Malignant neoplasms of respiratory and intrathoracic organs</i>							
Turin	City	11.2	13.2	41.9	63.4	3.7	4.8
	Rest of the province	8.7	14.2	37.8	48.5	4.3	3.4
Milan	City	14.6	22.4	38.9	70.2	2.7	3.1
	Rest of the province	10.7	17.1	42.6	73.3	4.0	4.3
Rome	City	16.3	23.9	43.8	65.3	2.7	2.7
	Rest of the province	12.5	19.9	46.0	69.7	3.7	3.5
Naples	City	13.8	16.1	55.3	69.9	4.0	4.4
	Rest of the province	9.2	10.4	53.2	77.9	5.8	7.5
Italy		9.6	13.7	38.5	56.4	4.0	4.1
<i>Total mortality (all causes)</i>							
Turin	City	333.6	1225.0	492.1	1603.9	1.5	1.3
	Rest of the province	362.4	1353.5	533.4	1800.9	1.5	1.3
Milan	City	309.2	1126.6	481.0	1588.9	1.6	1.4
	Rest of the province	323.1	1201.0	495.1	1622.7	1.5	1.4
Rome	City	336.0	1206.8	487.0	1559.1	1.4	1.3
	Rest of the province	375.8	1377.4	547.8	1741.1	1.5	1.3
Naples	City	433.1	1444.1	601.2	1736.0	1.4	1.2
	Rest of the province	451.5	1572.0	650.0	2005.4	1.4	1.3
Italy		349.9	1289.5	522.1	1708.5	1.5	1.3



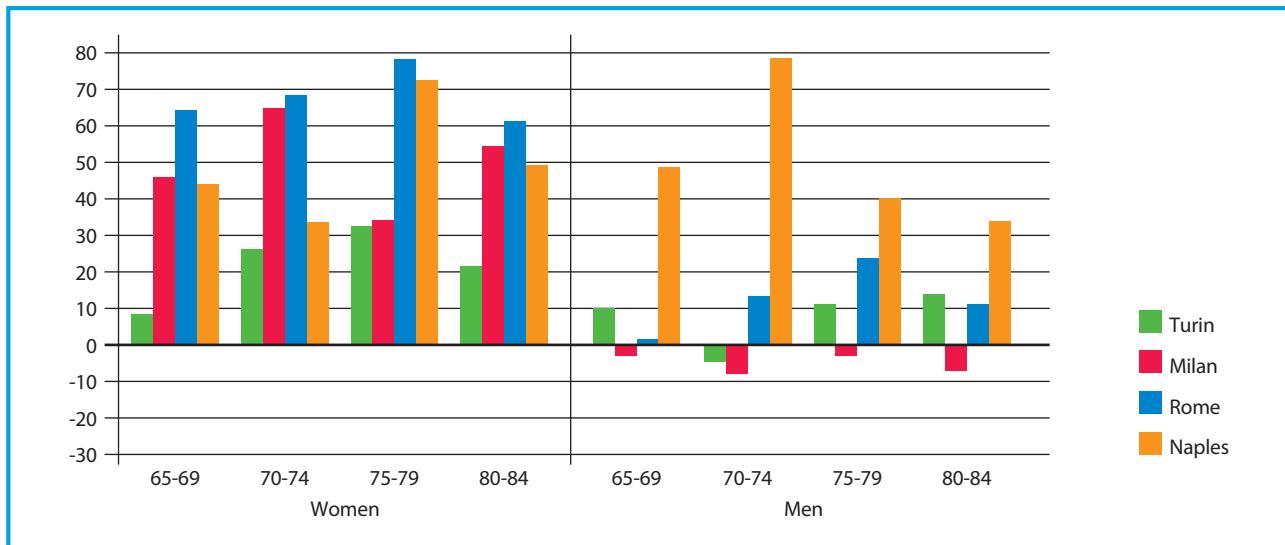
**Figure 1.** Percentage variations in mortality rates for malignant neoplasms of respiratory and intrathoracic organs (CRS) between city and rest of the province, and between city and national level, by gender and area of residence. Deaths at age 65 and over. Years 2014-2015.

**Table 2.** Mortality rates (per 10.000) for malignant neoplasms of respiratory and intrathoracic organs (CRS), by 5-year age group, gender and area of residence. Years 2014-2015.

Area of residence		Age			
		65-69	70-74	75-79	80-84
<i>Women</i>					
Turin	City	7.0	10.6	13.1	15.1
	Rest of the province	5.0	9.4	8.0	10.1
Milan	City	9.3	13.9	13.3	19.3
	Rest of the province	6.0	9.3	10.0	15.8
Rome	City	10.5	14.2	17.7	20.1
	Rest of the province	8.4	10.8	13.1	14.2
Naples	City	9.2	11.2	17.1	18.6
	Rest of the province	7.0	8.0	11.3	10.9
Italy		6.4	8.4	9.9	12.5
<i>Men</i>					
Turin	City	24.3	30.8	45.9	62.7
	Rest of the province	24.2	32.7	42.5	52.2
Milan	City	21.5	29.7	40.1	51.2
	Rest of the province	22.0	35.0	44.9	57.4
Rome	City	22.4	36.5	51.3	61.1
	Rest of the province	27.5	36.7	47.9	66.7
Naples	City	32.8	57.6	57.9	74.0
	Rest of the province	32.9	46.3	60.1	66.0
Italy		22.1	32.3	41.5	55.1



**Figure 2.** Percentage variations in mortality rates for malignant neoplasms of respiratory and intrathoracic organs (CRS) between city and rest of the province, by gender, 5-year age group and area of residence. Years 2014-2015.



**Figure 3.** Percentage variations in mortality rates for malignant neoplasms of respiratory and intrathoracic organs (CRS) between city and national level, by gender, 5-year age group and area of residence. Years 2014-2015.

inces compared to the cities. The comparative results for CRS mortality and total mortality in the two areas considered and for the two genders confirmed the assumptions of this study.

#### Gender gap

At national level, men over 65 years old had a CRS mortality rate four times greater than that among women (Table 1). As expected, the gender gap (male-to-female mortality rates) was lower in the four cities – 2.7 in Milan and Rome –, where the mortality of women over the age of 65 for this group of causes was higher than in the rest of the provinces and of Italy overall. The narrower gap between the two genders in cities was present in all age groups, except for those up to 74 years in Naples (Figure 4). Interestingly, with the exception of Naples, precisely the 65-69 years and 70-74 years age groups presented the lowest values of the gender gap. This result is in line with our hypothesis on cigarette smoking in women, and sees greater closeness between the two genders for the most recent cohorts (65-69 and 70-74 years) and a growing distance to the disadvantage of men for the oldest cohorts. Finally, the results in the provinces of Turin and Naples deserve particular attention, as the gender gap reaches there its highest levels, particularly in the older age groups, exceeding the value of 6 in the 80-84 years age group in the province of Naples.

With regard to total mortality, the gender gap was more or less equal in the cities and in the provinces and equal to the national value (Table 1).

#### 4. Discussion and conclusion

A summary of the most significant results shows, first of all, the disadvantage of women living in cities with CRS mortality rates that were substantially higher than in the rest of the provinces and in Italy overall. This result was also confirmed in an analysis by 5-year age groups. For men, by contrast, the territorial differences were limited and the inhabitants of cities were not always those who were more penalised than in the remaining areas of the provinces, as in the case of Milan and Rome.

Given the high female mortality rates observed in Tables 1 and 2 for CRS, the gender gap observed in cities in Figure 4 were lower than elsewhere. Obviously, by contrast the gender gap was higher in the rest of the provinces, where the male disadvantage reached its highest levels in the oldest age groups for Turin and Naples.

As already stated, interpreting these results is not easy on the basis of the data considered in our analysis. We would need much more information to explain the relation between risk factors and mortality. We began with the consideration that smoking and exposure to environmental pollution in urban areas was the basis of the results obtained, but we stressed our inability to distinguish the effects of the two risk factors.

It is well known that female smoking involved more recent cohorts, and, among those considered, women born after the 1940s, for whom smoking was a factor of emancipation among the more highly educated. According to official Istat figures for 2016, more educated women have the highest smoking habits both in metropolitan areas and in other large or small municipalities<sup>20</sup>. In fact, the percentage of smokers and ex-smokers among wom-

en over the age of 65 with at least a high school diploma was equal to 39% in metropolitan areas, almost 37% in municipalities with less than 10,000 inhabitants. Several Italian studies showed that during the 1980s and 1990s the prevalence of smoking and smoking-related diseases were directly related to education among women, and inversely related to education among men<sup>21-23</sup>.

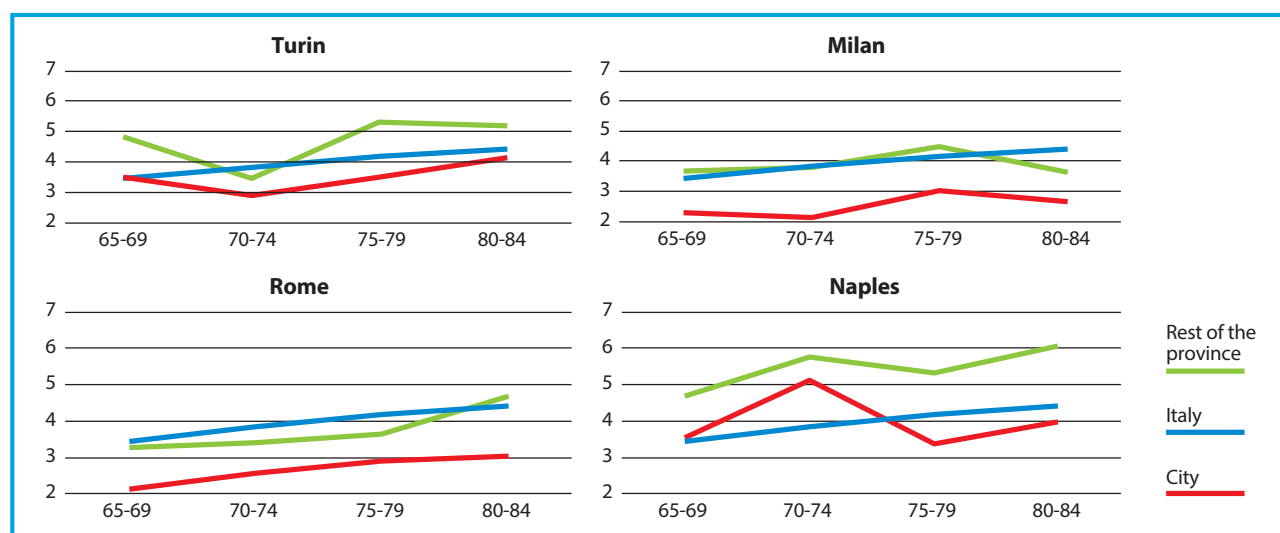
In the large cities, higher educational levels of women certainly encouraged more widespread smoking. From the figures of the most recent census of the population, in the four cities under consideration the percentage of women over the age of 60 in 2011 (65 and over in 2016) with at least high school diploma varies between 22% for Turin and 32% for Rome, compared with a national level of 17%<sup>24</sup>. It may be that these differences in educational levels are decisive for the differentials in smoking and, consequently, for the differentials in CRS mortality which in the city of Rome is up to 70% higher than the national level. Living and working in a large city created more stress due to the acquisition of social and working roles more similar to those of men. These, associated with greater insecurity for women in general, often led them to imitate male behaviours, including smoking.

Among men over the age of 65 the relation between educational level and smoking is different. In general, over the past few decades adult men were affected by a consistent decline in smoking prevalence<sup>25</sup>, with the most highly educated more affected by this decrease because of a greater awareness of the harm created by smoking and hence of the positive effects of greater prevention. Hence, as we have seen, in many cases the CRS mortality rate was lower in the city than in the rest of the province, where the lower educational level was probably associated with less prevention. One exception was the city of

Naples, where male mortality from this cause was higher than the rest of the province and, even more so, than Italy overall. In general, for the generations under study male disadvantage was certainly due in part to other factors such as greater exposure to professional risks typical of contact with toxic substances in manufacturing processes during the years of Italy's economic boom.

It is important to note that the different behavior of men and women produces gender differences that penalise women in the cities, reducing their distance from men for mortality due to this cause, and penalise men in the rest of the provinces, increasing their distance from women at every age.

Is it possible to think that the gaps in mortality due to this cause, which was also found for the oldest women in the cities, should be related only to different smoking habits and not to the harmful effects of environmental pollution in urban areas (presence and continual increase of PM<sub>10</sub> and PM<sub>2.5</sub>)? A recent and much broader study published by *Lancet Oncology* and carried out in 9 countries including Italy, clearly showed that for every increase of 5 µg/m<sup>3</sup> of PM<sub>2.5</sub>, the risk of lung cancer increases by 18%, while it grows by 22% for every increase of 10 µg/m<sup>3</sup> of PM<sub>10</sub><sup>26</sup>. The results of the study, which are part of the ESCAPE (European Study of Cohorts for Air Pollution Effects) project, concern persons of the same cohorts kept under observation for 13 years. Changes of residence and habits – smoking included – were registered for each person so as to relate the onset of any lung cancer with the degree of pollution in the areas they lived in, quite apart from other factors<sup>27</sup>. Given the evidence of these results, the International Agency for Research on Cancer (IARC) has included atmospheric pollution and fine particulate matters as one of the Class 1 substances that are certainly carcinogenic<sup>28</sup>.



**Figure 4.** Gender gap in mortality rates for malignant neoplasms of respiratory and intrathoracic organs (CRS) by 5-year age group and area of residence. Years 2014-2015.

It may be that for women the cumulative effect of exposure to smoking and pollution in urban areas is the basis for the large territorial differentials, given that women in these generations were not employed in industries with a marked health risk. It is also possible that for men the cumulative harmful effects of smoking and the working environment may make the contribution of the risks from urban pollution less evident. The risk factors certainly act individually, cumulating their negative effects on CRS mortality, but also jointly with each other, multiplying their effect and raising mortality levels even higher, though it is not possible to measure to what extent. Obviously, the cumulative effect also works on the levels of female mortality.

And finally, could it be that the harmful effects of *mal'aria* act differently on the two genders, penalizing women more? In other words, it could be that women are more sensitive to the effects of environmental pollution, particularly that part of it closely linked to traffic. For example, in an extensive follow-up study carried out on approximately 280,000 men and more than 180,000 women from eight States in the USA, aged 50-71 years at study baseline, Freedman et al. noted a significant increase in cases of lung cancer in female non-smokers, compared with male non-smokers, while no increased risk was found in women, whether smokers or ex-smokers, compared with men equally exposed<sup>29</sup>. Similar results were also found in other studies showing that

among never-smokers, women were twice as likely as men to develop lung cancer<sup>30,31</sup>.

In another study focused on which populations were most at risk of premature mortality induced by air pollution in the four largest US cities with the highest level of PM<sub>10</sub>, Zanobetti and Schwartz calculated the daily counts of deaths stratified by sex, race, and education in each city and investigated their associations with PM<sub>10</sub> in a Poisson regression model<sup>32</sup>. They then combined the results by using inverse variance weighting. They found evidence of effect modification by sex, with the slope in female deaths one third greater than in male deaths.

In the light of the many studies on the subject we can speculate that there really is a greater female sensitivity to be explained by external agents. Obviously, to verify this hypothesis, we need very detailed micro-statistical information and expertise other than that of the demographer. The interesting study by Vineis and Husgafvel-Pursiainen on large US and European cohorts goes in this direction<sup>33</sup>. The authors suggest that air pollution may increase lung cancer risk and that biomarkers can be useful to understand the mechanisms and to characterize high-risk groups.

Obviously, based on the data used in our paper, we have no answers to our questions. Data for cohorts, information on more cities, taking into account not only CRS mortality, but also mortality due to other causes, such as cardiovascular or cerebrovascular diseases, including information on environmental and individual risks, such as smoking, might help us develop statistical analyses to provide more information on the relationships between territorial pollution, smoking habits and mortality differences. Obviously, only follow-up epidemiological studies on individual samples can reveal the cause-effect relationships between the various risk factors and mortality, similar to the Cesaroni et al. or the Raaschou-Nielsen et al. studies<sup>7,26</sup>. In any case, we hope that studies on this topic will give greater attention to gender differences, so as to clarify some of the aspects identified here on the mortality of elderly women who are resident in the most polluted Italian cities.

### Key messages

- Exposure to fine particulate matter air pollution is an important risk factor for cancer of the respiratory system. Higher levels of average annual concentration of fine particulate matter are to be found in the major Italian cities of Turin, Milan, Naples and Rome compared to their European counterparts.
- Women over 65 years of age resident in the four major Italian cities present mortality rates for cancer of the respiratory system that are substantially higher than in the surrounding areas of the corresponding provinces and in Italy overall.
- For men of the same age, the territorial differences are limited and life in these cities is not always the main penalising factor. Their disadvantage in levels of mortality from this cause compared to women tends to decrease in the cities. It may be that impact of environmental pollution in urban areas differs in the two genders.
- Among the generations of women considered in the study, and especially those born after the 1940s, smoking represented a factor of emancipation that was mainly widespread among the more highly educated.
- Based on our data, we were not able to determine for women in the cities, who had higher educational levels, what role smoking habits and/or environmental pollution in urban areas played on their mortality rates.

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*Conflict of interest statement:* the Authors declare no conflicts of interest.

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