Effect of Air Pollution on Olfactory Function in Residents of Mexico City

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Abstract

To our knowledge there has been no study of the effect of everyday air pollution on olfactory function. It was therefore the aim of this study to compare the olfactory performance of long-term residents of Mexico City, an environment with high air pollution, with the olfactory performance of residents of the Mexican state of Tlaxcala, a region geographically similar to Mexico City but with low air pollution. Healthy volunteers [82 Mexico City subjects (MEX), 86 Tlaxcala subjects (TLX)] 20–63 years of age and balanced for age and gender between the two localities were tested for the perception of the odors of everyday beverages presented in squeeze bottles. When tested with ascending concentrations of stimuli in a three-way oddball paradigm, residents of Tlaxcala detected the odors of instant coffee and of an orange drink at significantly lower concentrations than residents of Mexico City. They also performed significantly better in discriminating between the two similar-smelling Mexican beverages horchata and atole in an oddball test. Significant differences between the two populations in overall olfactory performance were apparent in three of the four age classes (20- to 29-, 30- to 39-, and 40- to 49-year-old subjects) but not in the 50–63 years age class. About 10% of MEX subjects compared to about 2% of TLX subjects were judged to have poor olfactory function; all were from the older age classes (mean age: 48.6 years). Thus, air pollution in Mexico City appears to have a substantial impact on olfactory function even in young and middle-aged residents.

Key words: detection threshold, everyday odorants, odor discrimination, olfactory dysfunction

Introduction

Air pollution is a major problem in many large cities (Blake and Rowland, 1995; Mage *et al.*, 1996), and there is increasing evidence of the adverse effects of airborne contaminants on human health (Berglund *et al.*, 1992; Valverde *et al.*, 1997; Calderón-Garcidueñas *et al.*, 2000b, 2002, 2004). This includes damage to the nasal epithelium (Torjussen *et al.*, 1979; Hellquist *et al.*, 1983; Wilhelmsson and Lundh, 1984; Harkema *et al.*, 1987, 1999; Calderón-Garcidueñas *et al.*, 1992, 1998, 2000a, 2002), which is not surprising given the direct exposure of the nasal cavity to the external environment. Most reports, however, concern the respiratory epithelium from which it is easier to obtain biopsies than from the olfactory epithelium (Hastings and Miller, 2003). Nevertheless, there is also considerable evidence that exposure to airborne pollutants causes damage to the olfactory epithelium.

In frogs, exposure of the olfactory epithelium for even a few minutes to ether, chloroform, styrene, or toluene vapor results in increased secretory activity by sustacular cells,

in shortening or destruction of olfactory cilia, and results in a reduction in the electro-olfactogram (Ai and Takagi, 1963; Ekblom *et al.*, 1984). In rodents and dogs, exposure to airborne industrial compounds, ozone, and big-city air pollution also results in damage to the olfactory mucosa (Hurtt *et al.*, 1988; Keenan *et al.*, 1990; Nikula and Lewis, 1994; Brenneman *et al.*, 2000; Calderón-Garcidueñas *et al.*, 2002, 2003; reviewed in Hastings and Miller, 2003). However, few animal studies have investigated the consequences of such damage at the behavioral level (Hastings and Miller, 2003; but see Hurtt *et al.*, 1988; Apfelbach, 1991; Hastings *et al.*, 1991; Peele *et al.*, 1991; Youngentob *et al.*, 1997).

In humans, research has focused on the effects on olfactory function of volatiles in the workplace (reviewed in Cometto-Muñiz and Cain, 1991; Berglund *et al.*, 1992; Hastings and Miller, 2003). Impairment has been reported in workers exposed to high ambient levels of cadmium (Friberg, 1950; Potts, 1965; Yin-Zeng *et al.*, 1985; Rose *et al.*, 1992; Sulkowski

et al., 2000; Suruda, 2000), chromium (Watanabe and Fukuchi, 2000), irritant gases (Oka, 1981, cited in Hastings and Miller, 2003), acrylic acid and related substances (Schwartz *et al.*, 1989), sulfuryl fluoride (Calvert *et al.*, 1998), formaldehyde (Kilburn *et al.*, 1985; Holstrom and Wilhelmsson, 1988), and various solvents (Ahlström *et al.*, 1986; Sandmark *et al.*, 1989; Schwartz *et al.*, 1990). To our knowledge, however, there has been no study of the effect on olfactory function of the everyday air pollution characteristics of many large cities. Exposure to contaminants in experimental paradigms and the workplace is usually acute and thus may allow some degree of recovery. In contrast, exposure to general ambient air pollution is nearly continuous, raising the possibility that even relatively low levels of contamination might have significant long-term cumulative effects.

It was therefore our aim to test the olfactory function of residents of Mexico City—with over 20 million inhabitants and one of the highest levels of air pollution in the world (Blake and Rowland, 1995; Valverde *et al.*, 1997; Calderón-Garcidueñas *et al.*, 1998, 2000a, 2003)—and to compare this with the olfactory function of residents of Tlaxcala, a neighboring but less polluted Mexican state (Calderón-Garcidueñas *et al.*, 2002, 2003). We expected that subjects from Mexico City would have higher detection thresholds, poorer ability to describe and identify odorants, and poorer ability to discriminate between similar-smelling odorants than subjects from Tlaxcala.

Materials and methods

Subjects

In total, 168 healthy unpaid adult volunteers recruited from Mexico City and the state of Tlaxcala and balanced between the two locations with respect to age and gender were tested between March and July 2003 (Table 1). They were recruited according to 10-year age bins: 20–29, 30–39, 40–49 years, as well as an older group 50–63 years of age. Mexico City subjects (MEX) had lived all their life in Mexico City, and Tlaxcala subjects (TLX) had lived all their life in Tlaxcala or neighboring regions other than Mexico City. The two groups were similar in level of education and social background; subjects were students or staff, or family of students or staff at the Universidad Nacional Autónoma de México or at the Universidad Autónoma de Tlaxcala. None reported a history of respiratory disease or had a respiratory complaint at the time of testing, and all were engaged in relatively pollution-free indoor work. Although habitual smokers were excluded, 9% of TLX and 26% of MEX subjects reported that they smoked occasionally.

Odorants

Odor stimuli were popular beverages commercially available as water-soluble powders. We chose these in preference

Table 1   Origin, age, and gender of subjects

Age class	Mexico City		Tlaxcala	
	Women	Men	Women	Men
20–29	10	14	11	13
30–39	12	12	14	17
40–49	14	6	11	6
50–63	11	3	11	3
Total	47	35	47	39

to monomolecular substances to maximize the ecological validity of the stimuli and the ability of subjects to describe and accurately name them (Ayabe-Kanamura *et al.*, 1998; Distel and Hudson, 2001). Stimuli were prepared using purified bottled water (Bonafont, Liquimex, Estado de México, Mexico).

At the start of testing, three odorants were presented at a suprathreshold concentration to familiarize subjects with the test procedure: a strawberry drink (Clight, Kraft, Mexico City, Mexico; concentration 2.4 g/l), the hibiscus flower drink jamaica (Clight, Kraft; concentration 4.0 g/l), and a mango drink (Tang, Kraft; concentration 6.4 g/l). Two more odorants were used to determine olfactory thresholds, instant coffee (Nescafé Clasico, Nestlé, Mexico City, Mexico) and an orange drink (Clight, Kraft). Each was presented in an 11-step dilution series (coffee: step 1 concentration 1.9 g/l, dilution factor 51; orange: step 1 concentration 6.45 g/l, dilution factor 61). Finally, to test odor discrimination, a rice-based drink, horchata (Frescogary, D'gari, Estado de México, Mexico), and a similar-smelling maize-based drink, atole de cajeta (Maizena, Estado de México, Mexico), were used. Preliminary testing of an independent group of MEX subjects showed concentrations of 3.2 g/l of horchata and 4.4 g/l of atole to be approximately equal in intensity.

Stimuli were freshly prepared on the day of testing, and 25 ml of each were presented in 250-ml polyethylene squeeze bottles equipped with a plastic nozzle (Laska and Hudson, 1991). The lower third of each bottle was covered with masking tape to prevent subjects using visual cues to identify stimuli.

Test procedure

Subjects were tested alone in a well-ventilated room in a single session lasting approximately 20 min. All tests were conducted by the same person (A.A.), and each test had four parts:

Part 1. To familiarize subjects with the test situation and squeeze bottles, they were given bottles containing the strawberry, mango, and jamaica drinks and asked to describe and, if possible, to name them.

Part 2. To assess subjects' ability to detect odorants, they were presented with ascending concentrations of the instant coffee and the orange drink. At each concentration they were given three bottles, one containing the odorant and the other two containing water and were asked to identify the bottle that smelt different. They could sample each bottle only twice. Once subjects correctly identified the target bottle, they were retested with the previous (lower) concentration. If they twice identified the target at this concentration, it was taken as their detection threshold. If not, they were again presented with the higher concentration, and if they twice identified the target, this was taken as their threshold. If not, the next highest concentration was presented and so on.

Part 3. Testing continued by presenting the target bottles singly in ascending concentration and asking subjects to identify or describe the odor. The concentrations at which they could first describe an odor quality and then at which they could correctly identify the odorant were noted.

Part 4. Finally, to determine subjects' ability to distinguish between suprathreshold concentrations of two similar-smelling odorants, they were given 10 trials in which they were asked to distinguish between the odors of horchata and atole de cajeta. Subjects were presented with three bottles, one of which contained the target (five times horchata and five times atole in randomized order) and were asked to identify the bottle that smelt different.

Data analysis

Differences between the TLX and MEX groups were evaluated for each of the tests and according to the age classes in Table 1. In addition, an overall performance score was generated by ranking the threshold and discrimination values for each subject in each of the two groups, and from these an average percent rank was calculated. Following a Kolmogorov–Smirnov test, which showed the performance scores to be consistent with a normal distribution ($P = 0.70$), two-way analyses of variance (ANOVAs) by group and age class, before and after excluding smokers from the data, and by group and gender were performed using the statistical program StatView 4.5. Since TLX subjects were expected to perform better than MEX subjects, one-tailed tests were used to compare the scores of the two groups. $P \leq 0.05$ was taken as the level of significance throughout.

To identify subjects with particularly poor olfactory performance, a three-step elimination procedure was followed. First, subjects able to discriminate between horchata and atole above chance (≥ 7 of 10 trials correct; binomial test, $P < 0.05$) were excluded, then those able to identify both coffee and orange, and then those with detection thresholds for both coffee and orange below the population median.

Results

All subjects could perceive and most could describe the three stimuli during the familiarization procedure. In addition, 42% correctly named strawberry, 19% mango, and 19% jamaica. All provided detection threshold values for instant coffee and for the orange drink, 96% were able to describe an odor quality for coffee and 98% for orange, 82% could correctly identify coffee and 88% orange, and 55% could discriminate between horchata and atole above chance (≥ 7 of 10 trials correct).

On all tasks, TLX subjects performed better than MEX subjects; they detected the coffee and orange stimuli at significantly lower concentrations (median dilution steps 7 vs. 6 for coffee and 9 vs. 8 for orange; Mann–Whitney: $z = 2.64$, $P < 0.005$ and $z = 4.76$, $P < 0.0001$, respectively) and were significantly better in distinguishing between horchata and atole (median of correct responses: 7 vs. 6; Mann–Whitney: $z = 1.84$, $P < 0.033$; Figure 1).

A decline with age in the ability to detect the odors of coffee and orange was found in both groups (Figure 2, upper panels). For TLX subjects median thresholds for coffee increased from dilution step 8 to step 5, and for MEX subjects from dilution step 7 to step 5.5. Similarly, for TLX subjects median thresholds for orange increased from dilution step 10 to step 7, and for MEX subjects from dilution step 8 to step 6. Although the effect of age on the ability to discriminate the odors of horchata and atole was less marked, discrimination ability declined from a median of 7 out of 10 correct responses to a median of 6.5 and 6 correct responses for TLX and MEX subjects, respectively (Figure 2, bottom left panel). Accordingly, a two-way ANOVA on overall performance showed a significant effect of group [$F(1,160) = 14.1$, $P < 0.0002$] and age [$F(3,160) = 11.2$, $P < 0.0001$], and a significant interaction between group and age [$F(3,160) = 3.7$, $P < 0.01$]. Fisher protected least significant difference (PLSD) *post hoc* tests showed the age effect to be significant between all classes except the 40–49 and 50–63 year classes, and the difference between TLX and MEX subjects to be significant for all classes with the notable exception of the 50–63 year class (Figure 2, bottom right panel). Finally, the *post hoc* tests showed a significant decline in olfactory performance to occur earlier and more steeply in MEX than TLX subjects; when the 20–29 year class in each group was taken as the baseline and compared to the 30–39 year and 40–49 year classes, the decline was already significant in the 30–39 year and highly significant in the 40–49 year MEX subjects ($P < 0.05$ and $P < 0.0001$, respectively) compared to the corresponding TLX subjects ($P > 0.23$ and $P < 0.05$, respectively).

Removing the 29 subjects who reported smoking occasionally from the sample had little effect on the results. A two-way ANOVA on overall performance of nonsmoking subjects again showed significant effects of group [$F(1,131) = 15.7$, $P = 0.0001$] and age [$F(3,131) = 11.3$, $P < 0.0001$] and also a significant interaction between group and age
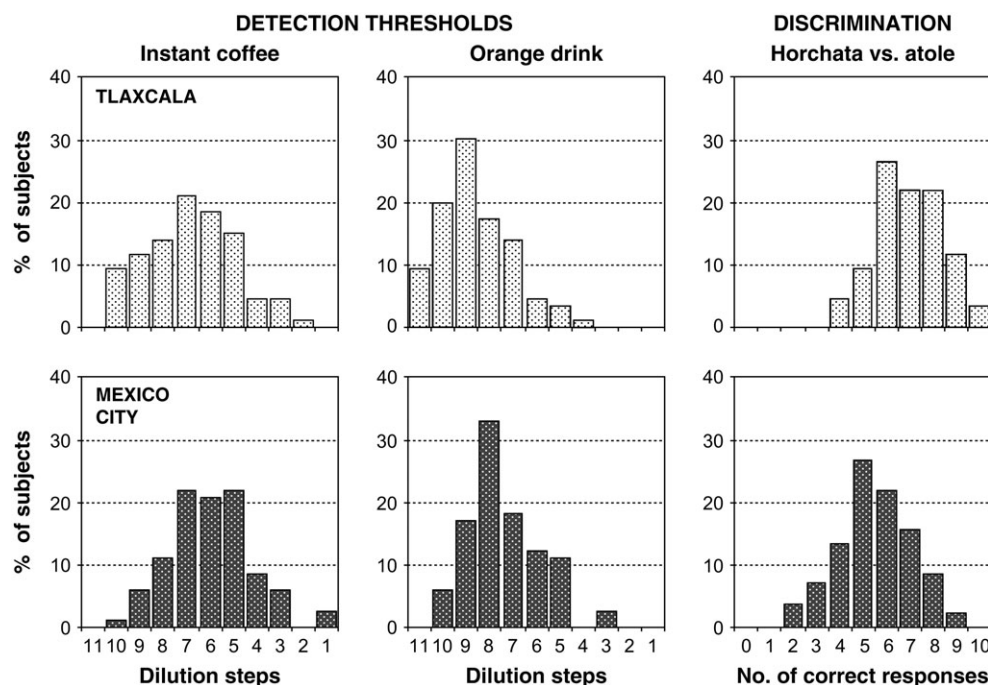
Figure 1 Olfactory performance by group. Light bars: subjects from Tlaxcala (*n* = 86); dark bars: subjects from Mexico City (*n* = 82). Left and middle panels: detection thresholds for the odors of instant coffee and orange drink. Right panel: ability to discriminate between the odors of two common Mexican beverages, horchata and atole. Bars give the number of respondents as percentage of the total number of subjects tested for each locality.

$[F(3,131) = 2.8, P < 0.05]$. Although the mean overall performance of men was better than of women (0.56 vs. 0.50), a two-way ANOVA by group and gender showed a significant effect for group $[F(1,164) = 16.3, P < 0.0001]$ but not for gender $[F(1,164) = 3.5, P > 0.06]$ and there was no interaction between group and gender $[F(1,164) = 0.51, P > 0.47]$.

With regard to the description of odor quality, there were no significant differences between TLX and MEX subjects in the number of dilution steps above threshold at which they first provided descriptors for the odors of coffee and orange (Mann–Whitney: $z = 1.79$, $P > 0.07$ and $z = 1.74$, $P > 0.15$, respectively; Figure 3, left panel). Similarly, with regard to identification of the two odorants, no significant differences were found between the two groups in the median concentrations needed, which were three to four dilution steps above the respective detection thresholds (Mann–Whitney: $z = 1.73$, $P > 0.08$ and $z = 0.02$, $P > 0.98$; Figure 3, right panel).

Finally, 10 subjects fulfilled our definition of poor olfactory performance, that is, they had detection thresholds for both coffee and orange above the population median, they were unable to discriminate between horchata and atole above chance, and they failed to correctly name either coffee or orange. All were older than 40 years, and only two were from Tlaxcala (both 50 years) compared to eight from Mexico City (mean age: 48.3 years). Neither of the TLX subjects and only two of the MEX subjects reported that they smoked.

Discussion

Taken together, the results support our prediction that long-term residents of Mexico City exposed to high daily levels of ambient air pollution would have impaired olfactory function compared to long-term residents of the state of Tlaxcala, a geographically similar region with low air pollution. Residents of Tlaxcala could detect the odors of instant coffee and orange drink at significantly lower concentrations than the residents of Mexico City, and they were significantly better in distinguishing between the odors of the two similar-smelling Mexican beverages horchata and atole. These results appear to be reliable since the difference between TLX and MEX subjects in overall olfactory performance was significant for three of the four age classes tested (Figure 2).

Although this study does not provide direct evidence that the poorer performance of the MEX subjects was due to damage to the olfactory epithelium from air pollution, it is the most likely explanation. First, the findings are consistent with reports of extensive damage to the respiratory and olfactory epithelium in humans and dogs living in Mexico City compared to humans and dogs living in other, less polluted Mexican cities (Calderón-Garcidueñas *et al.*, 1998, 2003). Second, the study design controlled for the influence of potentially important variables such as climate and altitude, age, gender and socioeconomic level of subjects, and of the experimenter by having the same person
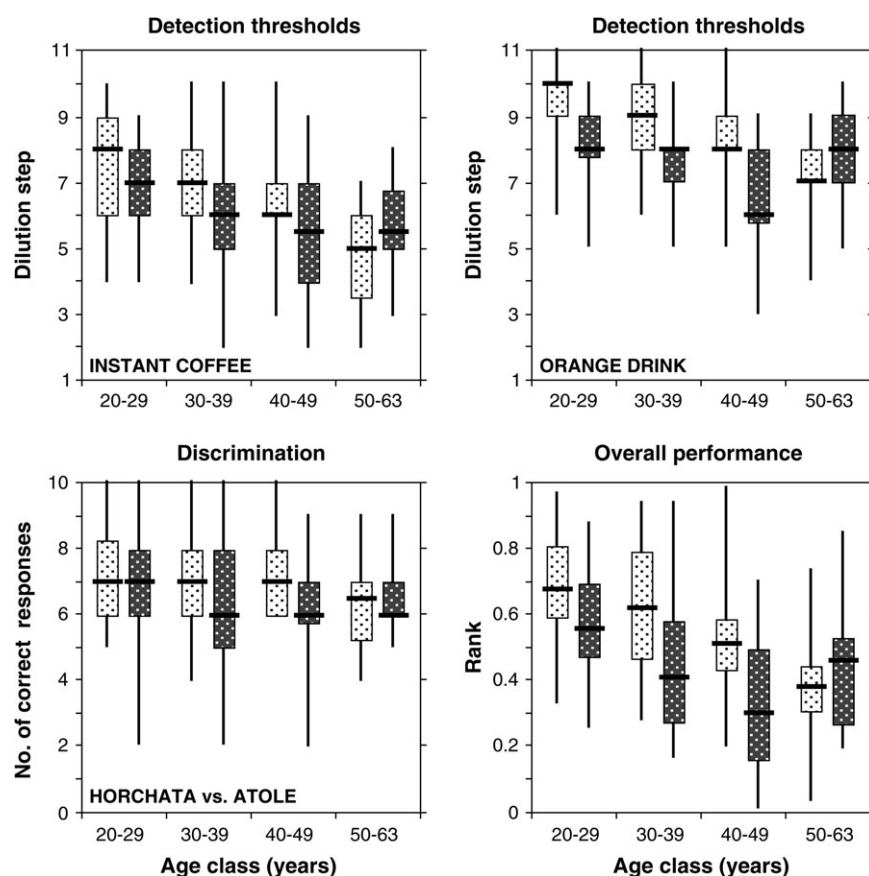
Figure 2 Olfactory performance by group and age class. Light bars: subjects from Tlaxcala; dark bars: subjects from Mexico City. Upper panels: detection thresholds; lower left panel: discrimination ability; lower right panel: overall performance (see Materials and Methods). Box plots: dark horizontal lines = medians, boxes = interquartile ranges, vertical lines = total ranges.
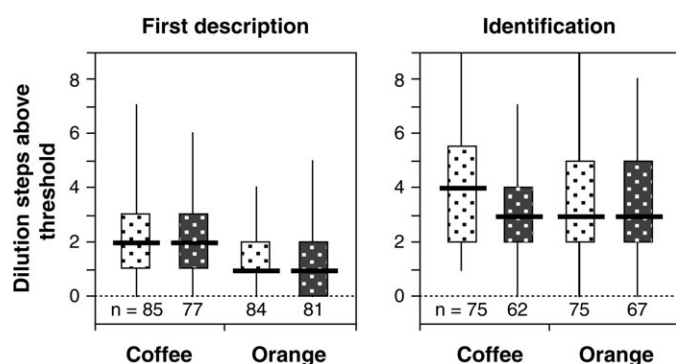

Figure 3 Dilution steps above threshold at which subjects were able to give a first description and to identify the odorants. Light bars: subjects from Tlaxcala ($n = 86$); dark bars: subjects from Mexico City ($n = 82$). Box plots: dark horizontal lines = medians, boxes = interquartile ranges, vertical lines = total ranges. The number of subjects from each group who could describe or identify the odorant is given below the bars.

administer all tests. And third, although more MEX than TLX subjects reported smoking occasionally, eliminating smokers from the analysis had little effect on the results.

A significant deficit in olfactory performance of MEX compared to TLX subjects was already apparent even in the 20- to 29-year-old participants, a finding consistent with reports of extensive damage to the upper airways in young adults and children living in Mexico City (Villarreal-Calderón et al., 2002). Unexpectedly, however, no significant difference was found between TLX and MEX subjects in the oldest age class. A possible explanation for this is the well-documented rise in ozone levels in Mexico City which occurred in 1986 after the introduction of a new type of gasoline (Calderón-Garcidueñas et al., 2000b).

Ozone is considered the most damaging pollutant in the atmosphere of Mexico City (Blake and Rowland, 1995; Calderón-Garcidueñas et al., 1998). Since outdoor concentrations are estimated to be 30–40% higher than indoor concentrations, damage to the upper airways in young adults and children has been attributed to their greater participation in outdoor activities, which often take place in the afternoon, the period of highest ozone contamination (Villarreal-Calderón et al., 2002). Thus, it is possible that in 1986 most of the 50- to 63-year-old subjects of the present study, at that time 33–46 years old and white-collar

professionals or housewives working indoors, were less exposed to high ozone levels than the present day younger subjects.

A significant decline in olfactory performance was found in the TLX control group already after the third decade. This was unexpected as studies of olfactory function across the life span have reported an age-dependent decline only after the fifth decade (Doty *et al.*, 1984; Wysocki and Gilbert, 1989; Lehrner *et al.*, 1999). There is no ready explanation for this early decline except that living at high altitudes may affect olfactory function more generally. This possibility should be taken into account when the performance of Mexico City residents is compared to the performance of residents of other highly polluted but lower altitude cities.

Finally, we may ask what is the relevance of these findings to the everyday life of residents of Mexico City? At fist glance it seems that they should have few problems in using their sense of smell since the detection thresholds and discrimination abilities of most MEX subjects were well within the range of the TLX control group. Although this may seem surprising, it is consistent with animal studies showing that extensive lesions to the olfactory epithelium or olfactory bulbs have little effect on olfactory performance (Hudson and Distel, 1987; Lu and Slotnick, 1998; Slotnick *et al.*, 2000). Nevertheless, 9.8% of MEX compared to 2.3% of TLX subjects were judged by our criteria to have poor olfactory function. This is certainly a conservative estimate given that subjects were drawn from an academic population, worked indoors, and had a good standard of living and health care. Furthermore, younger Mexico City residents, presently exposed to higher levels of ozone during outdoor life than previous generations, may experience a severe decline in olfactory function 10–20 years into the future. For a megacommunity like Mexico City with more than 20 million inhabitants, this could constitute an important public health issue.

Acknowledgements

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