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# Mammographic density in the environs of multiple industrial sources

**Authors:**

Tamara Jiménez[a], Marina Pollán[b,c], Alejandro Domínguez-Castillo[b], Pilar Lucas[b], María Ángeles Sierra[b,c], Adela Castelló[b,c], Nerea Fernández de Larrea-Baz[b,c], David Lora-Pablos[d,e,f], Dolores Salas-Trejo[c,g,h], Rafael Llobet[i], Inmaculada Martínez[g,h], Marina Nieves Pino[j], Mercedes Martínez-Cortés[j], Beatriz Pérez-Gómez[b,c], Virgina Lope[b,c,*,1], and Javier García-Pérez[b,c,1]

**Author´s afiliations:**

[a] Department of Preventive Medicine, Public Health and Microbiology, *Universidad Autónoma de Madrid (UAM)*, Madrid, Spain

[b] Cancer and Environmental Epidemiology Unit, Department of Epidemiology of Chronic Diseases, National Center for Epidemiology, Carlos III Institute of Health (*Instituto de Salud Carlos III)*, Madrid, Spain

[c] Consortium for Biomedical Research in Epidemiology & Public Health (*CIBER en Epidemiología y Salud Pública – CIBERESP*), Spain

[d] Scientific Support Unit, *Instituto de Investigación Sanitaria Hospital Universitario 12 de Octubre* (imas12), Madrid, Spain

[e] Spanish Clinical Research Network (SCReN), Madrid, Spain

[f] Faculty of Statistical Studies, *Universidad Complutense de Madrid* (UCM), Madrid, Spain

[g] Valencian Breast Cancer Screening Program, General Directorate of Public Health, Valencia, Spain

[h] Center for Public Health Research CSISP, FISABIO, Valencia, Spain

[i] Institute of Computer Technology, Universitat Politècnica de València, Valencia, Spain

[j] *Servicio de Prevención y Promoción de la Salud, Madrid Salud, Ayuntamiento de Madrid,* Madrid, Spain

***Corresponding author:**

Virginia Lope
Cancer and Environmental Epidemiology Unit
Department of Epidemiology of Chronic Diseases
National Center for Epidemiology
Carlos III Institute of Health
Avda. Monforte de Lemos, 5, 28029 Madrid, Spain
Tel.: +34-918222640
E-mail: **vicarvajal@isciii.es**

[1]**Joint senior authors**

**E-mail addresses:**
TJ: tamarajc91@gmail.com
MP: mpollan@isciii.es
AD-C: a.dominguez@isciii.es
PL: pmlucas@isciii.es
MAS: masierra@isciii.es
AC: acastello@isciii.es
NFL-B: nfernandez@isciii.es
DL-P: david@h12o.es
DS-T: salas_dol@gva.es
RL: rllobet@dsic.upv.es
IM: martinez_inm@gva.es
MNP: pinoemn@madrid.es
MM-C: martinezcme@madrid.es
BP-G: bperez@isciii.es
VL: vicarvajal@isciii.es
JG-P: jgarcia@isciii.es

## HIGHLIGHTS:

- First assessment on mammographic density (MD) and multiple industrial sources
- Two approaches used to identify industrial clusters associated to a higher MD
- Increased MD with the proximity to an increasing number of industrial sources
- 6 industrial clusters with a higher MD in their environs were identified in Madrid

## Abstract

**Background:** Mammographic density (MD), defined as the percentage of dense fibroglandular tissue in the breast, is a modifiable marker of the risk of developing breast cancer. Our objective was to evaluate the effect of residential proximity to an increasing number of industrial sources in MD.

**Methods:** A cross-sectional study was conducted on 1225 premenopausal women participating in the DDM-Madrid study. We calculated distances between women´s houses and industries. The association between MD and proximity to an increasing number of industrial facilities and industrial clusters was explored using multiple linear regression models.

**Results:** We found a positive linear trend between MD and proximity to an increasing number of industrial sources for all industries, at distances of 1.5 km (*p*-trend=0.055) and 2 km (*p*-trend=0.083). Moreover, 62 specific industrial clusters were analyzed, highlighting the significant associations found between MD and proximity to the following 6 industrial clusters: cluster 10 and women living at ≤1.5 km (β=10.78, 95% confidence interval (95%CI)=1.59; 19.97) and at ≤2 km (β=7.96, 95%CI=0.21; 15.70); cluster 18 and women residing at ≤3 km (β=8.48, 95%CI=0.01; 16.96); cluster 19 and women living at ≤3 km (β=15.72, 95%CI=1.96; 29.49); cluster 20 and women living at ≤3 km (β=16.95, 95%CI=2.90; 31.00); cluster 48 and women residing at ≤3 km (β=15.86, 95%CI=3.95; 27.77); and cluster 52 and women living at ≤2.5 km (β=11.09, 95%CI=0.12; 22.05). These clusters include the following industrial activities: surface treatment of metals/plastic, surface treatment using organic solvents, production/processing of metals, recycling of animal waste, hazardous waste, urban waste-water treatment plants, inorganic chemical industry, cement and lime, galvanization, and food/beverage sector.

**Conclusions:** Our results suggest that women living in the proximity to an increasing number of industrial sources and those near certain types of industrial clusters have higher MD.

**Key words:** Breast density; Breast cancer; Industrial cluster; Industry; Industrial pollution.

**Abbreviations:** MD, Mammographic density; BMI, Body mass index; EDCs, Endocrine disrupting chemicals; IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant

Release and Transfer Register; 95%CI: 95% confidence interval; SD, standard deviation; PAHs, Polycyclic aromatic hydrocarbons; TSP, total suspended particulate matter; POPs, Persistent organic pollutants; $PM_{10}$, particulate matter with a diameter between 2.5 and 10 µm; $PM_{2.5}$, particulate matter <2.5 µm.

## 1. Introduction

In 2020, breast cancer was the most diagnosed cancer worldwide (Sung et al., 2021). In Spain, 34,088 new cases were estimated, representing 31% of all cancer cases in women (European Commission, 2022). Mammographic density (MD), defined as the amount of dense fibroglandular tissue (composed of epithelial and stromal elements) compared with the amount of fatty tissue (Lester et al., 2022), is the main phenotype marker for breast cancer risk. It has been described that women with a MD greater than 75% have almost 4 times more risk of developing breast cancer (Bond-Smith and Stone, 2019) and it is also the factor with the highest attributable fraction (Assi et al., 2012). The risk attributable to high MD appears to be greater in premenopausal women (accounting for approximately one-third of breast tumors in white, Hispanic, and Asian women) than in postmenopausal women (with risks between 13-14%) (Bissell et al., 2020).

Like some other modifiable risk factors for breast cancer, MD has the potential to change throughout women's life (Lester et al., 2022). There is evidence that MD decreases progressively with age, with the transition to menopause, with the number of children and with the body mass index (BMI). In contrast, the use of hormone replacement therapy, particularly treatments that combine estrogen and progesterone, appears to increase it (Assi et al., 2012; Huo et al., 2014).

Some environmental exposures, such as exposure to traffic or to specific pollutants (pesticides, dioxins, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls), have been associated with breast cancer risk (Gray et al., 2017; Hiatt and Brody, 2018; Rodgers et al., 2018), but fewer studies have analyzed their association with MD (Eslami et al., 2022). Outdoor air pollution (a complex mixture of pollutants originating from natural and anthropogenic sources) was classified as carcinogenic to humans by the International Agency for Research on Cancer (International Agency for Research on Cancer, 2016), and industrial facilities are responsible for the release of many of these known and suspected human carcinogens (Fernández-Navarro et al., 2017). Previous studies have shown that women living in urban areas, with high levels of air pollution, have higher breast density (Emaus et al., 2014; Perry et al., 2008). Moreover, industries release endocrine disrupting chemicals (EDCs), which can alter the development of the mammary gland (Fenton, 2006; Mandrup et al., 2015). In this sense, higher MD has been observed in women exposed to cobalt and lead (White et al., 2019), in girls and adolescents with high levels of phthalates in urine (Binder et al., 2018) or in women with high levels of urinary magnesium (Mora-Pinzon et al., 2018).

In relation to exposure to industrial pollution sources, the epidemiological studies involving individual data often use the distance from the participant's residence to the industrial facility as a proxy of exposure (García-Pérez et al., 2019; Hii et al., 2022; Pan et al., 2011). However, industries are usually grouped into industrial clusters, so independent analyses of each single industrial source may not give a realistic picture of the exposure. In this sense, some authors consider that most pollutants are highly correlated to each other, so that an additive or synergic effect cannot be excluded and, consequently, single pollutant models may be difficult to interpret (Billionnet et al., 2012). On the other hand, in relation to cumulative and multiple exposures, some authors have assessed the impact of multipollutant air exposures and breast cancer risk, suggesting that multipollutant approaches are more precise than single pollutant models (Amadou et al., 2020). Moreover, in a recent study that assessed the relationship between breast cancer and exposure to several mixtures of metals, the authors found that the concentrations of these mixtures were different in women with breast cancer and those without cancer, which could be due to synergistic or antagonistic effects between metals (Mérida-Ortega et al., 2022). Accordingly, it would be interesting to assess the increased risk of chronic diseases near industrial areas with multiple pollutant sources, where the population is exposed to different sources and complex mixtures of toxic substances released into the environment (Cocozza et al., 2021; García-Pérez et al., 2012; Ramis et al., 2011).

In a previous study of our group, we detected potential associations between higher MD and residential proximity to certain industrial sectors and plants releasing specific pollutants, in a sample of Spanish premenopausal women (Jiménez et al., 2022). Now, in the present paper, we have deepened in the study of MD and its relationship with industrial pollution, using methodological approaches whose application in this field is novel, with the purpose of: 1) assessing the possible increase in MD with the proximity to an increasing number of industrial sources (for all industries jointly and according to industrial sectors), and 2) identifying industrial clusters with higher MD in women living in their environs.

## 2. Materials and methods

### 2.1 Study population

DDM-Madrid is a cross-sectional study that recruited 1466 Spanish premenopausal women (39-50 years) at the Medical Diagnostic Centre of Madrid City Council (*Madrid Salud*), between June 2013 and May 2015, where they attended for their routine gynecological examination (Jiménez et al., 2021; Lope et al., 2020). Women were invited to participate in the study by phone, and 88% agreed to collaborate. The DDM-Madrid study was conducted in accordance with the Declaration of Helsinki guidelines, was formally approved by the Ethics and Animal Welfare Committee of the Carlos III Institute of Health, and all participants signed an informed consent.

### 2.2 Data collection

Trained interviewers administered a face-to-face epidemiological questionnaire, which included sociodemographic information, personal and family medical background, gynecological, obstetric and occupational history, physical activity, tobacco smoking and alcohol consumption. Dietary information was collected through a validated self-fulfilled semiquantitative food frequency questionnaire (Vioque et al., 2013).

Percent MD was measured from the digital cranio-caudal mammographic images of the left breast using DM-Scan, a free semi-automated computer tool to measure MD that has shown high validity and reproducibility (Llobet et al., 2014).

Data about industrial pollution sources located in the study area were provided by the Spanish Ministry for the Ecological Transition and the Demographic Challenge. These industrial sources include facilities governed by the Integrated Pollution Prevention and Control (IPPC) Directive and installations pertaining to industrial activities not subject to IPPC but included in the European

Pollutant Release and Transfer Register (European Environment Agency, 2022). In our analyses, we included all industries releasing pollutants (to air and water) with emission amounts >0 kg/year (i.e., all industries, not only those exceeding a certain established threshold for some pollutant). The locations of each industry and women's postal addresses were geocoded and validated, prior to performing the analyses, into Universal Transverse Mercator ED50 zone 30 N coordinates, using a previously published methodology (García-Pérez et al., 2019).

### 2.3. Statistical analyses

After excluding 24 women with analogical images, 17 participants whose MD could not be measured, 24 without available address, and 176 women with missing data in the covariates used in the analyses, the final sample size was based on 1225 participants.

The main characteristics of the women were summarized with absolute values and percentages. MD, in relation to these characteristics, was described using arithmetic means, their 95% confidence intervals (95%CIs), and standard deviations (SDs). Moreover, two-sided Chi-square test was used to compare descriptive characteristics between women residing at ≤3 km from any industrial source and women residing at >3 km.

We calculated Euclidean distances between industries and women´s residences. We considered as proximity ("exposure") to industrial sources those zones with women living at ≤'D' km from any industrial source, taking into account several distances 'D' (1.5, 2, 2.5, and 3 km) to calculate buffers around each installation. The reference zone was consisted of areas with women residing at >3 km from any industrial source.

Two methodological approaches were used to evaluate this association, using multivariable linear regression models to estimate β coefficients and their 95%CIs. All analyses were adjusted for potential confounders associated with MD (Huo et al., 2014) and proximity to industrial sources (García-Pérez et al., 2018). These variables were: age (continuous), previous breast biopsies (yes/no), family history of breast cancer (none, second degree, first degree), BMI (continuous), oral contraceptives use (never, past use, current use), smoking (never, former smoker, current smoker), alcohol consumption (0, <10g/d, ≥10 g/d), number of children (0, 1, 2, >2), education (primary school or less, secondary school, university graduate) and energy intake (continuous). To carry out the analyses, we used:

1) First methodological approach (to assess the possible increase in MD with the proximity to an increasing number of industrial sources): for each distance 'D', we categorized the proximity variable as follows: "1 source", if the woman resided at ≤'D' km from 1 industrial facility; "2 sources", if the woman resided at ≤'D' km from 2 industrial facilities; 3 sources", if the woman resided at ≤'D' km from 3 industrial facilities; "≥4 sources", if the woman lived at ≤'D' km from 4 or more industrial facilities; and "0 sources" (reference), if the woman resided at >3 km from any industrial source. This approach was applied to all industries jointly (an independent model for each distance), and according to industrial sectors (an independent model for each distance and industrial sector). *P*-value for linear trend (*p*-trend) was calculated including the proximity variable as continuous.

2) Second methodological approach (to identify industrial clusters with higher MD in women living in their environs): in the first step, with the purpose of selecting areas of proximity to multiple industrial sources, we applied the multivariate technique of cluster analysis to the industrial installations using the "agglomerative hierarchical clustering" method and the Euclidean distance (in meters) between the industries as the metric (Hair Jr. et al., 2019). The following linkage criteria were proposed: complete, average, single, Ward, median, centroid, and McQuitty/WPGMA linkage clustering. For the linkage method with the highest correlation between the industrial locations (in our case, it corresponded to the "average linkage clustering", with a Pearson's r=0.967), we obtained the industrial clusters cutting the dendrogram into several groups of industries by specifying a cut height of 3000. In the second step, for each of the obtained industrial clusters, we calculated buffers (considering the previously established distances 'D' between 1.5 and 3 km) around each installation belonging to the industrial cluster under study. Finally, in the third step, we evaluated the relationship between MD and proximity (for all distances 'D') to each industrial cluster by means of multivariable linear regression models, where the proximity variable for each woman was categorized as: a) "near" the industrial cluster, if the woman lived at ≤'D' km

from the industrial cluster under study; b) “intermediate area, if the woman resided at ≤3 km from any industrial cluster other than the analyzed cluster; and c) “far” from the industrial cluster (reference area), if the woman resided at >3 km from any industrial installation.

Lastly, with the purpose of introducing robustness in our analysis, a sensitivity analysis including only women living in their current domicile for ≥2 and ≥10 years was performed.

All analyses were performed using R 4.0.2 software.

## 3. Results

A total of 1225 premenopausal women were included in the analyses. The main characteristics are shown in Table 1. Mean age of participants was 44±2.8 years old, and most of them had no previous breast biopsies (89.2%), had no family history of breast cancer (77.2%), had a normal BMI (67.0%), used oral contraceptives in the past (58.3%), were ex-smokers or never smokers (74.4%), consumed ≤10 grams per day of alcohol (85.7%), had two children or more (52.1%), and had completed a university degree (61.4%). Lastly, regarding the time that the participants had been living at their current domicile, our study population proved to be enough stable, with 95.1% of participants living in their current residence for ≥2 years, and 62.9% for ≥10 years.

Participants had a mean MD of 34.82% (SD=17.28), being higher in younger women, in women with previous breast biopsies, in those who never used oral contraceptives, in participants with lower BMI, in those with university graduate, and in nulliparous. On the other hand, in relation to the proximity (≤3 km *vs.* >3 km) to industrial sources, the number of women with overweight or obesity (BMI≥25) was significantly higher in those living at ≤3 km from any industrial source (*p*-value=0.001); on the contrary, the number of women with high alcohol consumption (≥10 g/day) and with university studies was higher in those living at >3 km from any industry (*p*-values=0.009 and <0.001, respectively).

In relation to the association between MD and number of industrial sources in the proximity of the residence (first methodological approach), for all industries jointly (Figure 1), the results showed a growing and positive trend, for distances of 1.5 ($\beta_{1\ source}$=1.09, $\beta_{2\ sources}$=2.59, $\beta_{3\ sources}$=2.86, $\beta_{\geq 4\ sources}$=8.37, *p*-trend=0.055) and 2 km ($\beta_{1\ source}$=1.03, $\beta_{2\ sources}$=0.06, $\beta_{3\ sources}$=2.28, $\beta_{\geq 4\ sources}$=5.56, *p*-trend=0.083). The remaining distances studied (2.5 and 3 km) showed smaller effects and a less clear trend (*p*-trends=0.114 and 0.132, respectively). Similar results were obtained in the sensitivity analyses considering only women living in their current domicile for ≥2 years (see Supplementary Data, Figure S1) and ≥10 years (see Supplementary Data, Figure S2), highlighting the positive trends observed for a distance of 1.5 km (*p*-trends=0.060 (Supplementary Data, Figure S1), and 0.040 (Supplementary Data, Figure S2)). With respect to the analysis according to industrial sectors (data not shown), the only result of interest corresponded to "urban waste-water treatment plants", where women (n=37) who resided near (≤3 km) 1 single source belonging to this industrial sector showed a higher MD (β=2.21; 95%CI: (-3.07; 7.48), and women (n=5) living near 2 sources showed a β=8.00 (95%CI: (-5.99; 22.00)), *p*-trend=0.192.

Regarding the results for industrial clusters (second methodological approach), the cluster analysis using the "average linkage clustering" criterion revealed 62 industrial clusters, and the corresponding dendrogram is shown in Figure 2. On the other hand, Figure 3 shows the geographical distribution of women's residences, as well as the 154 individual industries grouped by the 62 industrial clusters (along with an example of proximity areas for a distance of 1.5 km). The association between MD and residential proximity to industrial clusters with statistically significant results and a number of participants ≥5 is shown in Table 2. Significant associations were observed between:

a) cluster 10 (industries 1996 (Production and processing of metals), 1568 and 6563 (Surface treatment of metals and plastic), and 3380 and 6557 (Surface treatment using organic solvents)) and women living at ≤1.5 km (β=10.78; 95%CI=1.59; 19.97) and at ≤2 km (β=7.96; 95%CI=0.21; 15.70);

b) cluster 18 (industries 3337, 3389, and 4195 (Surface treatment of metals and plastic), 1678 and 2032 (Hazardous waste), 1978 (Disposal or recycling of animal waste), and 6717 (Urban waste-water treatment plants)) and women residing at ≤3 km (β=8.48; 95%CI=0.01; 16.96);

c) cluster 19 (industries 3507 and 5967 (Surface treatment of metals and plastic), and 1651 (Inorganic chemical industry)) and women living at ≤2.5 km, that were the same as those living at ≤3 km (β=15.72; 95%CI=1.96; 29.49);

d) cluster 20 (industry 1662 (Cement and lime)) and women living at ≤3 km (β=16.95; 95%CI=2.90; 31.00);

e) cluster 48 (industries 7736 (Galvanization), and 5437 (Surface treatment of metals and plastic)) and women residing at ≤3 km (β=15.86; 95%CI=3.95; 27.77); and

f) cluster 52 (industries 6558 (Production and processing of metals), 6729 (Urban waste-water treatment plants), and 6553 (Food and beverage sector)) and women living at ≤2.5 km (β=11.09; 95%CI=0.12; 22.05).

Note that all the abovementioned results correspond to increases in percentages of MD above 5%, which we considered as relevant from an epidemiologic standpoint. However, due to the small sample size of women residing in areas close to the industrial clusters, we must be cautious with the conclusions obtained from these results.

All these industrial clusters are located in the province of Madrid. Supplementary Data, Table S1 shows detailed information of the industries constituting the industrial clusters with significant results, including year of commencement of operations, industrial sector, municipality, and pollutants released to air and water.

## 4. Discussion

This study analyses the relationship between MD, a main biomarker of breast cancer risk, and residential proximity to multiple industrial sources. We have applied two methodological approaches to deepen in the study of MD and its relationship with industrial pollution, refining the exposure assessment with respect to multiple industrial installations. In summary, our results point towards an increase in MD with the proximity to an increasing number of industrial sources (jointly), particularly for distances of 1.5 and 2 km. Furthermore, we have detected a non-statistically significant increase in MD in women living at ≤3 km to 2 urban waste-water treatment plants, and among women living in the environs of six industrial clusters located in the province of Madrid.

In a previous study (Jiménez et al., 2022), we analyzed this association taking into account the distance between the woman's residence and the industrial facility as a single pollutant source, focusing the attention on "individual" sources. Now, in the present paper, we have applied alternative approaches focusing the attention on exposure to multiple industrial sources, giving a more realistic view of the possible relationship between MD and industrial exposures.

It is important to emphasize the importance and insights gained from using the cluster analysis in the second methodological approach applied in our study. This analytical technique has allowed us to identify clusters formed by industrial facilities located very close spatially in our study area. This is very useful when there are a large number of industries in a specific area and these industries need to be classified into a small number of mutually exclusive groups based on the similarities (distances) among the installations with the purpose of carrying out more specific studies in their environs. Using this technique, we have detected six potential industrial clusters of interest, in relation to a higher MD in women residing in their environs. This scientific base can help environmental and health authorities to carry out more specific studies in the vicinity of these industrial clusters.

In relation to the study of multiple ambient exposures, some papers have focused the attention on the characterization and identification of multiple pollution sources (Amiri et al., 2019; Cocozza et al., 2021; Coker et al., 2016; Han et al., 2020; Riccardi et al., 2008). On the other hand, some authors have proposed new approaches to the study of multi-pollutant exposure profiles associated with health effects (Huang et al., 2018; Oakes et al., 2014; Taylor et al., 2016; Zanobetti et al., 2014; Zhu et al., 2019). Regarding cancer, some authors have found increased risks of cancer mortality in populations close to multiple industrial sources (Ancona et al., 2015; Bauleo et al., 2019; García-Pérez et al., 2012; Ramis et al., 2011). In the specific case of breast cancer, a population-based case-control study conducted in New York (US) considered the impact on the incidence of this tumor from multiple sources of PAHs, showing associations with exposure to indoor sources, not with outdoor air pollution (White et al., 2016).

To the best of our knowledge, this is the first attempt to study the relationship between proximity to multiple industrial sources and MD. On the one hand, our results showed an increase in MD associated with residential proximity to a growing number of industrial sources, with an almost significant trend at distances less than or equal to 1.5 and 2 km. This approach could be interpreted as a proxy or surrogate of a “dose-response” analysis.

By industrial sectors, this association was stronger for the “urban waste-water treatment plants”. In our previous study (Jimenez et al., 2022), a higher MD with residential proximity (≤3 km) to installations belonging to this sector was also detected (β=3.19). Now, in the present paper, our results showed an increase in MD from β=2.21 (in women residing at ≤3 km of one waste-water treatment plant) to β=8.00 (in women residing at ≤3 km of two waste-water treatment plants), suggesting cumulative effects in the environmental exposure that could explain this trend observed in our results. Although there are no epidemiological studies assessing MD or breast cancer risk in women living in the environs of these installations, it is known that urban waste-water and sewage treatment plants release some carcinogens to air (e.g., total suspended particulate matter (TSP) (see Supplementary Data, Table S1)), and pollutants that have been related to higher MD (nitrogen dioxide (Eslami et al., 2022)) or breast cancer risk (nitrogen dioxide and carbon monoxide) (Batyrova et al., 2021; Cheng et al., 2022; Wei et al., 2021). Moreover, the effluents of these plants contain EDCs that can alter the development of the mammary gland (Fenton, 2006; Mandrup et al., 2015). Therefore, a more detailed exposure assessment of specific pollutants released by this type of installations is necessary to confirm our findings.

In relation to the analysis of specific industrial clusters, we have detected some industrial zones with higher MD in women who live in their environs. These clusters are grouped by industries belonging to different industrial sectors: metal industry (production and processing of metals, galvanization, surface treatment of metals and plastic), cement, inorganic chemical industry, waste management (hazardous waste, disposal or recycling of animal waste, and waste-water treatment plants), food/beverage sector, and surface treatment using organic solvents (see Supplementary Data, Table S1). Clusters of several industries located in large industrial areas could entail high concentrations of individual pollutants and complex mixtures of substances released to air, water, and soil (Satpathy et al., 2020; Yadav et al., 2022; Zhu et al., 2022). In this sense, several authors have assessed carcinogenic health risks associated with exposure to toxic substances in residents close to industrial clusters, with mixed results showing both moderate and high cancer risks (Ahamad et al., 2021, 2020; Chabukdhara and Nema, 2013; Vega et al., 2021).

Pollutants released to air and water by the installations constituting the industrial clusters of our study (Supplementary Data, Table S1) include EDCs, and other known and suspected carcinogens, such as persistent organic pollutants (POPs), PAHs, particulate matter or metals. With regard to certain POPs, a cross-sectional study found a positive association between levels of serum bisphenol A and MD in postmenopausal women (Sprague et al., 2013). Another cross-sectional study found higher MD in young women with high serum PCB levels (Rusiecki et al., 2020). However, Diorio et al. found no association with plasma levels of this contaminant in postmenopausal women (Diorio et al., 2013). With respect to PAHs, a prospective cohort study of mother-daughter pairs conducted in New York City (US) found limited evidence of an overall association between exposure to certain ambient PAHs during pregnancy and breast tissue composition in adolescent daughters and their mothers (Kehm et al., 2022). However, when the authors stratified by household smoke during pregnancy, they found that PAHs exposure was associated with higher MD. White et al. also found higher odds of dense breasts in women living in areas with higher PAH exposure. However, this association appeared to be driven by confounding with other air toxics (White et al., 2019). In relation to particulate matter, the installations of our study released particulate matter with a diameter between 2.5 and 10 µm ($PM_{10}$) and TSP. The studies existing in the literature about MD and exposure to particulate matter have focused, mainly, on particulate matter with a diameter < 2.5 µm ($PM_{2.5}$), showing inconsistent results: in a large population-based screening registry, the researchers found a positive association between MD and $PM_{2.5}$ (Yaghjyan et al., 2017), whereas in the Nurse's Health Study cohorts conducted in the US, the authors did not find associations between $PM_{2.5}$ and $PM_{10}$ exposures and MD (DuPre et al., 2017). Finally, regarding metals exposure, a cross-sectional study published in 2019 showed that women living near to high concentrations of lead and cobalt had higher MD, being this result stronger in premenopausal women (White et al., 2019).

With respect to the limitations of our study, due to its cross-sectional nature, we cannot investigate possible changes in MD across time. On the other hand, a critical aspect is the small number of women living near the industrial clusters with statistically significant results in our study (Table 2), so we must be cautious with the interpretation of these results. However, the findings in relation to the high MD found in women close to some clusters (with increases in percentages of MD >15%) support the need for further epidemiological research on these industries. Another aspect to consider is that all women were recruited from a single center in Madrid City, limiting the generalizability of findings and causing a possible selection bias (for instance, excluding women who had a private insurance and did not attend to the gynecological examination offered by the public health service). Moreover, some covariates were self-reported and thus might have been subject to recall bias. Despite adjusting for a wide variety of potential confounders, residual confounding cannot be completely excluded. Finally, we used Euclidean distances between industrial sources and women´s residences as a surrogate of the “real” exposure to the industrial pollution, assuming an isotropic model, something that could lead to a potential problem of misclassification.

On the other hand, among the main strengths of this study are the high participation rate and its novelty. This is the first attempt to analyze the possible association between MD and proximity to multiple industrial sources, applying different methodological approaches to refine the exposure assessment to industrial pollution. Another important strength is that we analyzed the Spanish facilities included in the (IPPC+E-PRTR) register, a public and exhaustive inventory of industrial installations releasing toxic pollutants in the EU. With respect to outcome measurement, mammograms were obtained in a single center, with the same equipment and in the context of routine clinical practice, and MD was quantified on a continuous scale, using a validated computer-assisted method (Llobet et al., 2014), and by a single reader with high internal consistency. Finally, the inclusion of a sensitivity analysis considering participants residing in their current residence for ≥2 and ≥10 years has provided a more comprehensive description of the possible association between MD and proximity to multiple industrial sources.

## 5. Conclusion

Since MD is considered as an intermediate phenotype for breast cancer that can be modified by environmental factors, more epidemiological studies are needed to furnish in-depth knowledge of potential risk factors related to a higher MD. In this study, we have used methodological approaches whose application in this field (MD and its relationship with industrial pollution) is novel, refining the exposure assessment with respect to multiple industrial sources. The associations found between increased MD (main phenotype risk marker of breast cancer) and residential proximity to an increasing number of industrial installations and specific industrial clusters suggest a contribution of these pollutant sources in the genesis of breast cancer, highlighting the need to design specific regulations to reduce the impact of their activity in the population's health. These findings support the need for further research on identification and control of pollutant sources related to MD.

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**Figure 1**. Association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly. Note that vertical axes are not in the same scale in the four graphics.

**Figure 2**. Cluster dendrogram showing the industrial clusters obtained using the “average linkage clustering” method.

**Figure 3.** Geographical distribution of women’s residences (green points), as well as industries (black symbols) grouped by the 62 industrial clusters and their proximity areas for 1.5 km buffers around each industry. Note that the proximity areas for each industrial cluster are in different colors and, for those clusters with statistically significant results showed in Table 2, their names are in red color and the names of the municipalities are in blue color.

**Table 1.** Descriptive characteristics of the study population.

| | All women | | | Women residing at ≤3 km from any industrial source | | | Women residing at >3 km from any industrial source | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mammographic density (%) | | | Mammographic density (%) | | | Mammographic density (%) | | |
| **Characteristic** | **n (%)** | **Mean (95%CI)** | **SD[a]** | **n (%)** | **Mean (95%CI)** | **SD[a]** | **n (%)** | **Mean (95%CI)** | **SD[a]** | ***p*-value[b]** |
| Total | 1225 (100.0) | 34.82 (33.85; 35.79) | 17.28 | 726 (100.0) | 34.36 (33.10; 35.62) | 17.27 | 499 (100.0) | 35.49 (33.97; 37.01) | 17.30 | |
| Age (years) | | | | | | | | | | 0.299 |
| <45 | 654 (53.4) | 36.14 (34.82; 37.46) | 17.22 | 397 (54.7) | 35.72 (34.06; 37.37) | 16.79 | 257 (51.5) | 36.81 (34.62; 38.99) | 17.88 | |
| ≥45 | 571 (46.6) | 33.30 (31.89; 34.72) | 17.24 | 329 (45.3) | 32.72 (30.81; 34.64) | 17.71 | 242 (48.5) | 34.09 (32.00; 36.18) | 16.59 | |
| Previous breast biopsies | | | | | | | | | | 0.891 |
| No | 1093 (89.2) | 33.94 (32.93; 34.95) | 17.07 | 649 (89.4) | 33.50 (32.21; 34.80) | 16.87 | 444 (89.0) | 34.57 (32.96; 36.18) | 17.35 | |
| Yes | 132 (10.8) | 42.14 (39.17; 45.10) | 17.41 | 77 (10.6) | 41.57 (37.34; 45.80) | 18.94 | 55 (11.0) | 42.92 (38.92; 46.92) | 15.14 | |
| Family history of breast cancer | | | | | | | | | | 0.423 |
| None | 946 (77.2) | 35.00 (33.91; 36.08) | 17.07 | 563 (77.5) | 34.97 (33.55; 36.39) | 17.18 | 383 (76.8) | 35.03 (33.34; 36.73) | 16.92 | |
| Second degree only | 192 (15.7) | 34.73 (32.15; 37.31) | 18.27 | 117 (16.1) | 32.97 (29.78; 36.16) | 17.60 | 75 (15.0) | 37.48 (33.16; 41.79) | 19.06 | |
| First degree | 87 (7.1) | 33.11 (29.43; 36.78) | 17.48 | 46 (6.3) | 30.40 (25.47; 35.32) | 17.04 | 41 (8.2) | 36.15 (30.74; 41.55) | 17.67 | |
| Body mass index (kg/m$^2$) | | | | | | | | | | 0.001 |
| <18.5 | 20 (1.6) | 41.74 (33.84; 49.64) | 18.03 | 6 (0.8) | 37.98 (27.13; 48.83) | 13.56 | 14 (2.8) | 43.35 (32.94; 53.76) | 19.87 | |
| 18.5-24.9 | 821 (67.0) | 39.12 (37.98; 40.26) | 16.64 | 468 (64.5) | 39.35 (37.83; 40.87) | 16.74 | 353 (70.8) | 38.81 (37.08; 40.53) | 16.52 | |
| 25-29.9 | 278 (22.7) | 27.53 (25.84; 29.23) | 14.41 | 178 (24.5) | 27.51 (25.48; 29.54) | 13.81 | 100 (20.0) | 27.57 (24.54; 30.61) | 15.48 | |
| ≥30 | 106 (8.7) | 19.35 (16.80; 21.89) | 13.37 | 74 (10.2) | 18.98 (15.93; 22.02) | 13.36 | 32 (6.4) | 20.21 (15.52; 24.91) | 13.55 | |
| Use of oral contraceptives | | | | | | | | | | 0.314 |
| Never | 473 (38.6) | 36.70 (35.08; 38.31) | 17.92 | 268 (36.9) | 35.73 (33.64; 37.81) | 17.40 | 205 (41.1) | 37.97 (35.43; 40.51) | 18.55 | |
| Past use | 714 (58.3) | 33.79 (32.55; 35.02) | 16.82 | 436 (60.1) | 33.70 (32.07; 35.32) | 17.29 | 278 (55.7) | 33.92 (32.03; 35.81) | 16.08 | |
| Current use | 38 (3.1) | 30.89 (25.82; 35.96) | 15.94 | 22 (33.0) | 30.83 (24.81; 36.84) | 14.39 | 16 (3.2) | 30.97 (21.99; 39.96) | 18.35 | |
| Tobacco consumption | | | | | | | | | | 0.687 |
| Never | 483 (39.4) | 35.54 (33.96; 37.13) | 17.74 | 284 (39.1) | 34.76 (32.72; 36.79) | 17.49 | 199 (39.8) | 36.66 (34.15; 39.18) | 18.08 | |
| Former smoker | 429 (35.0) | 34.57 (32.99; 36.16) | 16.74 | 261 (36.0) | 34.80 (32.69; 36.92) | 17.43 | 168 (33.7) | 34.21 (31.85; 36.58) | 15.65 | |
| Current smoker | 313 (25.6) | 34.04 (32.13; 35.96) | 17.31 | 181 (24.9) | 33.09 (30.66; 35.53) | 16.71 | 132 (26.5) | 35.35 (32.26; 38.43) | 18.10 | |
| Alcohol consumption (g/day) | | | | | | | | | | 0.009 |
| 0 | 248 (20.2) | 34.07 (31.89; 36.26) | 17.56 | 157 (21.6) | 32.89 (30.27; 35.50) | 16.72 | 91 (18.3) | 36.12 (32.25; 39.99) | 18.84 | |
| <10 | 802 (65.5) | 34.98 (33.79; 36.18) | 17.30 | 483 (66.5) | 34.79 (33.22; 36.34) | 17.50 | 319 (63.9) | 35.29 (33.42; 37.15) | 17.03 | |
| ≥10 | 175 (14.3) | 35.14 (32.64; 37.63) | 16.87 | 86 (11.9) | 34.68 (31.08; 38.27) | 16.99 | 89 (17.8) | 35.58 (32.08; 39.08) | 16.84 | |
| Number of children | | | | | | | | | | 0.141 |
| 0 | 306 (25.0) | 37.86 (35.82; 39.90) | 18.20 | 166 (22.9) | 37.88 (35.31; 40.46) | 16.94 | 140 (28.1) | 37.83 (34.57: 41.08) | 19.65 | |
| 1 | 280 (22.9) | 35.81 (33.68; 37.95) | 18.23 | 176 (24.2) | 36.60 (33.83; 39.37) | 18.77 | 104 (20.8) | 34.48 (31.16; 37.80) | 17.28 | |
| 2 | 576 (47.0) | 33.00 (31.67; 34.33) | 16.26 | 349 (48.1) | 31.88 (30.15; 33.61) | 16.48 | 227 (45.5) | 34.71 (32.66; 36.77) | 15.80 | |
| >2 | 63 (5.1) | 32.32 (28.55; 36.10) | 15.29 | 35 (4.8) | 31.10 (26.29; 35.92) | 14.55 | 28 (5.6) | 33.85 (27.81; 39.89) | 16.30 | |
| Education | | | | | | | | | | <0.001 |
| Primary school or less | 52 (4.2) | 31.33 (26.42; 36.24) | 18.05 | 43 (5.9) | 30.34 (24.79; 35.88) | 18.55 | 9 (1.8) | 36.06 (25.93; 46.20) | 15.51 | |
| Secondary school | 421 (34.4) | 33.40 (31.82; 34.99) | 16.61 | 286 (39.4) | 33.86 (31.89; 35.84) | 17.06 | 135 (27.1) | 32.43 (29.79; 35.06) | 15.62 | |
| University graduate | 752 (61.4) | 35.85 (34.60; 37.11) | 17.54 | 397 (54.7) | 35.15 (33.46; 36.85) | 17.24 | 355 (71.1) | 36.64 (34.78; 38.50) | 17.85 | |
| Energy intake (Kcal/day)[c] | | | | | | | | | | 0.115 |
| <1674.8 | 408 (33.3) | 33.68 (31.98; 35.37) | 17.47 | 225 (31.0) | 33.26 (30.94; 35.58) | 17.76 | 183 (36.7) | 34.19 (31.70; 36.67) | 17.13 | |
| 1674.8-2151.1 | 409 (33.4) | 35.74 (34.07; 37.40) | 17.18 | 252 (34.7) | 34.88 (32.78; 36.99) | 17.01 | 157 (31.4) | 37.11 (34.39; 39.83) | 17.41 | |
| >2151.1 | 408 (33.3) | 35.04 (33.38; 36.71) | 17.18 | 249 (34.3) | 34.82 (32.70; 36.94) | 17.09 | 159 (31.9) | 35.39 (32.69; 38.09) | 17.37 | |
| Women living in their current residence for ≥2 years | 1165 (95.1) | 34.82 (33.83; 35.82) | 17.31 | 689 (94.9) | 34.31 (33.01; 35.60) | 17.31 | 476 (95.4) | 35.57 (34.02; 37.13) | 17.29 | 0.800 |
| Women living in their current residence for ≥10 years | 771 (62.9) | 34.95 (33.71; 36.18) | 17.52 | 466 (64.2) | 34.60 (33.00; 36.21) | 17.64 | 305 (61.1) | 35.47 (33.53; 37.42) | 17.33 | 0.302 |

[a] Standard deviation.

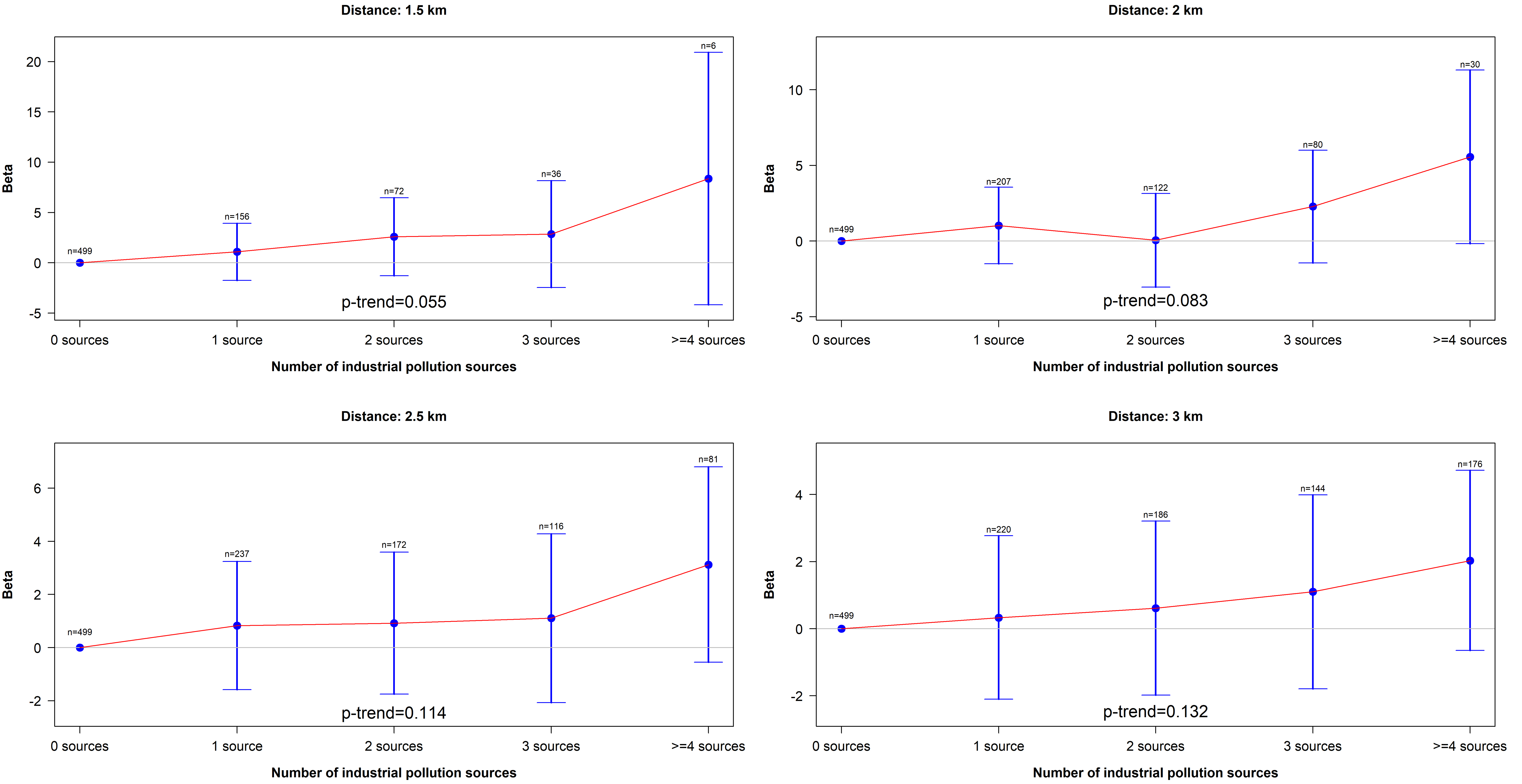
[b] Two-sided Chi-square test was used to compare descriptive characteristics between women residing at ≤3 km from any industrial source and women residing at >3 km.

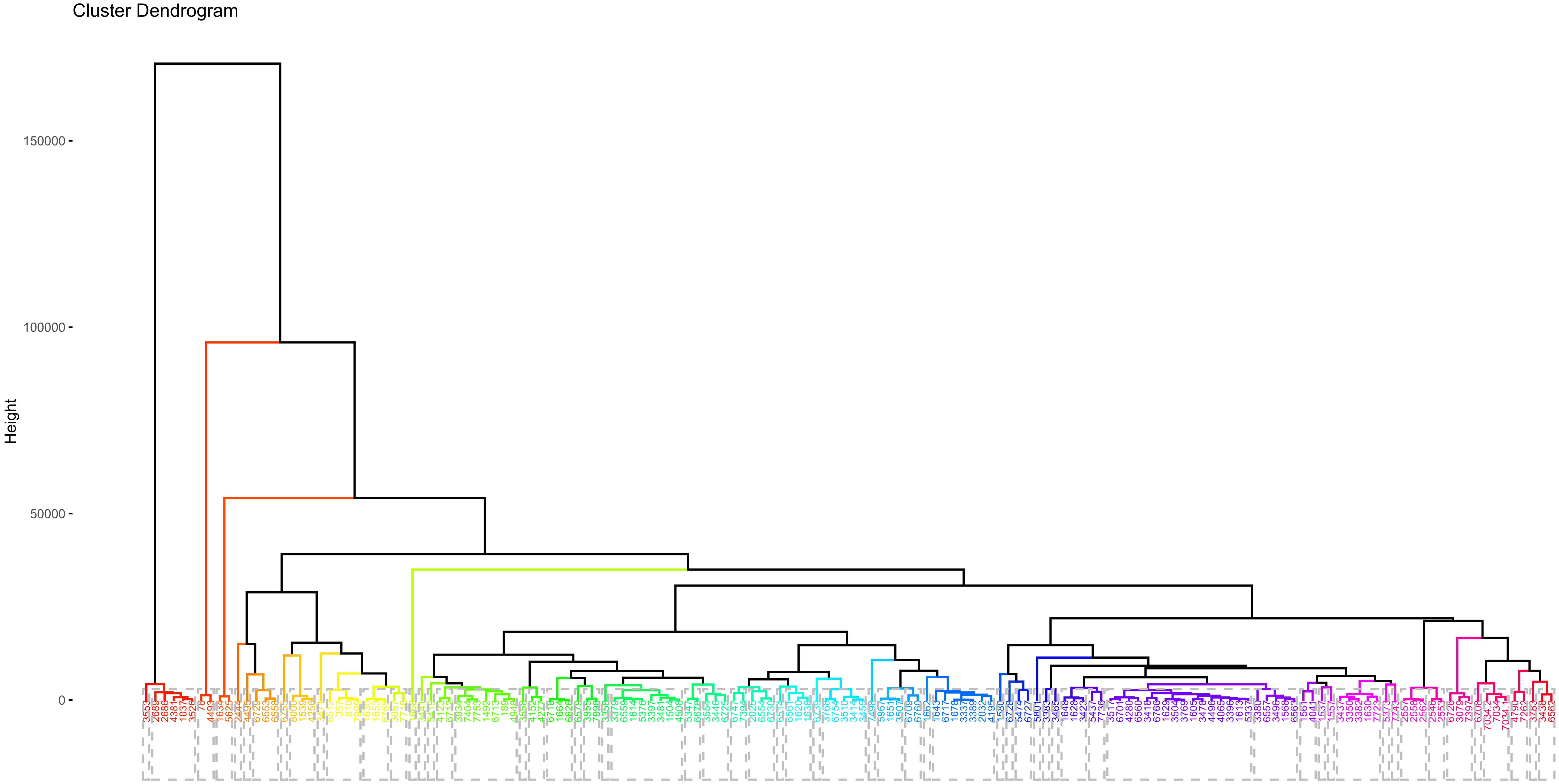
[c] Variable in tertiles.

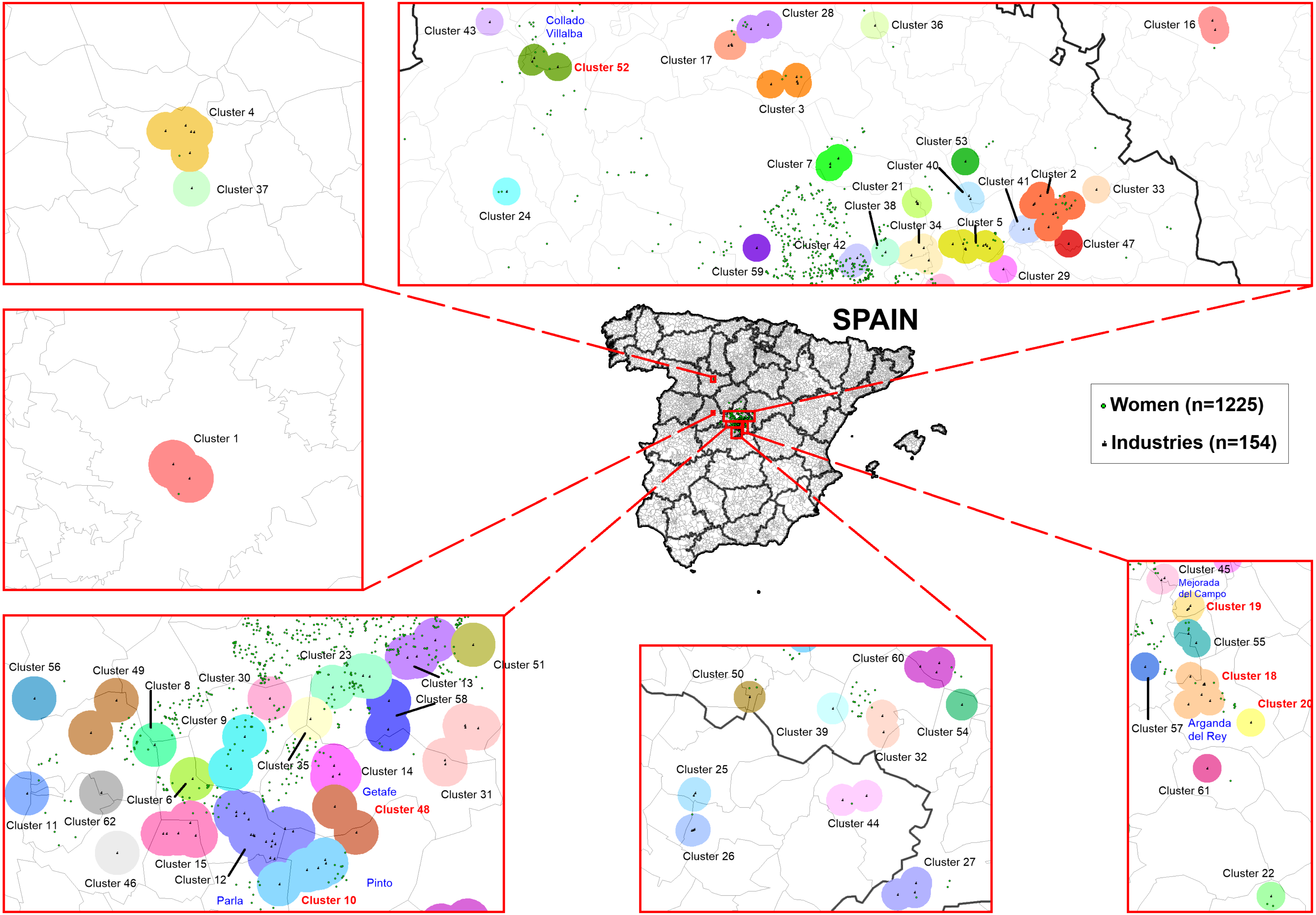
**Table 2.** Association between mammographic density and residential proximity to industrial clusters with statistically significant results and a number of participants ≥5. Statistically significant results are highlighted in bold.

| | Women residing at ≤1.5 km | | | Women residing at ≤2 km | | | Women residing at ≤2.5 km | | | Women residing at ≤3 km | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clusters - PRTR codes and industrial sectors | n | $\beta^a$ | 95%CI | n | $\beta^a$ | 95%CI | n | $\beta^a$ | 95%CI | n | $\beta^a$ | 95%CI |
| *Cluster 10*: 1996 (Production and processing of metals), 1568 and 6563 (Surface treatment of metals and plastic), and 3380 and 6557 (Surface treatment using organic solvents) | 12 | **10.78** | **(1.59; 19.97)** | 17 | **7.96** | **(0.21; 15.70)** | 22 | 6.67 | (-0.22; 13.56) | 23 | 5.99 | (-0.75; 12.72) |
| *Cluster 18*: 3337, 3389, and 4195 (Surface treatment of metals and plastic), 1678 and 2032 (Hazardous waste), 1978 (Disposal or recycling of animal waste), and 6717 (Urban waste-water treatment plants) | <5 | | | 6 | 0.21 | (-12.51; 12.92) | 8 | 6.44 | (-4.68; 17.56) | 14 | **8.48** | **(0.01; 16.96)** |
| *Cluster 19*: 3507 and 5967 (Surface treatment of metals and plastic), and 1651 (Inorganic chemical industry) | <5 | | | <5 | | | 5 | **15.72** | **(1.96; 29.49)** | 5 | **15.72** | **(1.96; 29.49)** |
| *Cluster 20*: 1662 (Cement and lime) | <5 | | | <5 | | | <5 | | | 5 | **16.95** | **(2.90; 31.00)** |
| *Cluster 48*: 7736 (Galvanization), and 5437 (Surface treatment of metals and plastic) | <5 | | | <5 | | | <5 | | | 7 | **15.86** | **(3.95; 27.77)** |
| *Cluster 52*: 6558 (Production and processing of metals), 6729 (Urban waste-water treatment plants), and 6553 (Food and beverage sector) | <5 | | | 6 | 10.39 | (-2.28; 23.05) | 8 | **11.09** | **(0.12; 22.05)** | 9 | 7.9 | (-2.44; 18.23) |

[a] Adjusted for age, previous breast biopsies, family history of breast cancer, body mass index, oral contraceptives use, smoking, alcohol consumption, parity, education and energy intake.


Distance: 1.5 km
Beta
20
15
10
5
0
-5
n=499
n=156
n=72
n=36
n=6
p-trend=0.055
0 sources
1 source
2 sources
3 sources
>=4 sources
Number of industrial pollution sources
Distance: 2 km
Beta
10
5
0
-5
n=499
n=207
n=122
n=80
n=30
p-trend=0.083
0 sources
1 source
2 sources
3 sources
>=4 sources
Number of industrial pollution sources
Distance: 2.5 km
Beta
6
4
2
0
-2
n=499
n=237
n=172
n=116
n=81
p-trend=0.114
0 sources
1 source
2 sources
3 sources
>=4 sources
Number of industrial pollution sources
Distance: 3 km
Beta
4
2
0
-2
n=499
n=220
n=186
n=144
n=176
p-trend=0.132
0 sources
1 source
2 sources
3 sources
>=4 sources
Number of industrial pollution sources


Cluster Dendrogram
Height
150000
100000
50000
0


SPAIN
● Women (n=1225)
▲ Industries (n=154)
Cluster 4
Cluster 37
Cluster 43
Collado Villalba
Cluster 52
Cluster 28
Cluster 17
Cluster 3
Cluster 36
Cluster 16
Cluster 24
Cluster 7
Cluster 53
Cluster 40
Cluster 21
Cluster 38
Cluster 41
Cluster 2
Cluster 33
Cluster 34
Cluster 5
Cluster 42
Cluster 59
Cluster 47
Cluster 29
Cluster 1
Cluster 56
Cluster 49
Cluster 8
Cluster 30
Cluster 23
Cluster 13
Cluster 51
Cluster 58
Cluster 9
Cluster 35
Cluster 14
Getafe
Cluster 48
Cluster 31
Cluster 6
Cluster 11
Cluster 62
Cluster 15
Cluster 12
Cluster 46
Parla
Cluster 10
Pinto
Cluster 50
Cluster 60
Cluster 39
Cluster 54
Cluster 32
Cluster 25
Cluster 44
Cluster 26
Cluster 27
Cluster 45
Mejorada del Campo
Cluster 19
Cluster 55
Cluster 18
Cluster 20
Cluster 57
Arganda del Rey
Cluster 61
Cluster 22

# Supplementary Data

Title of the manuscript: “Mammographic density in the environs of multiple industrial sources”

This document is available as supplementary data for inclusion as online documentation. It includes:

Table S1, showing information of the industries constituting the industrial clusters with significant results in the analysis of Table 2, including the PRTR code, year of commencement of operations, industrial sector, location (province and municipality), and pollutants released to air and water.

Figure S1, showing the association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly, and for the sensitivity analysis with only women residing in their current residence for ≥2 years. Note that vertical axes are not in the same scale in the four graphics.

Figure S2, showing the association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly, and for the sensitivity analysis with only women residing in their current residence for ≥10 years. Note that vertical axes are not in the same scale in the four graphics.

Table S1: information of the industries constituting the industrial clusters with significant results in the analysis of Table 2, including the PRTR code, year of commencement of operations, industrial sector, location (province and municipality), and pollutants released to air and water.

| Cluster | PRTR code | Year[a] | Industrial sector[b] | Province | Municipality | Pollutants released to air | Pollutants released to water |
|---|---|---|---|---|---|---|---|
| 10 | 1568 | 1988 | 2.f | Madrid | Pinto | Carbon monoxide; carbon dioxide; chromium; nickel; zinc; chlorine; TSP[c] | Total nitrogen; phosphorus; copper; nickel; zinc; halogenated organic compounds; TOC[d]; chlorides; fluorides; COD[e] |
| 10 | 3380 | 1989 | 9.c | Madrid | Parla | Carbon monoxide; carbon dioxide; dichloromethane; nitrogen oxides; TOC[d] | TOC[d]; COD[e] |
| 10 | 3496 | 1996 | 2.e | Madrid | Pinto | Carbon monoxide; carbon dioxide; copper; lead; dioxins + furans; chlorine; TSP[c]; TOC[d] | |
| 10 | 6557 | 1963 | 9.c | Madrid | Pinto | Carbon monoxide; carbon dioxide; TOC[d] | Total nitrogen; phosphorus; copper; mercury; nickel; lead; zinc; TOC[d]; naphthalene; phenols; PAHs[f]; chlorides; fluorides; COD[e] |
| 10 | 6563 | 1998 | 2.f | Madrid | Pinto | Chlorine | Total nitrogen; chromium; copper; nickel; halogenated organic compounds; naphthalene; toluene; chlorides; phosphorus; zinc; trichloromethane; TOC[d]; cyanides; fluorides; COD[e] |
| 18 | 1643 | 1978 | 5.e | Madrid | Arganda del Rey | Methane; carbon monoxide; carbon dioxide; ammonia; NMVOC[g]; nitrogen oxides; sulfur oxides; dioxins + furans; PAHs[f]; $PM_{10}$[h] | Nitrogen; phosphorus; dioxins + furans; chlorides; TOC[d]; COD[e] |
| 18 | 1678 | 1986 | 5.a | Madrid | Arganda del Rey | Methane; carbon monoxide; carbon dioxide; nitrogen oxides; sulfur oxides; dichloromethane; tetrachloroethylene; trichloroethylene; PAHs[f]; TSP[c]; TOC[d]; | TOC[d]; COD[e] |
| 18 | 2032 | 1997 | 5.a | Madrid | Arganda del Rey | Carbon monoxide; carbon dioxide; nitrogen oxides | Total nitrogen; phosphorus; mercury; TOC[d]; COD[e] |
| 18 | 3337 | 1986 | 2.f | Madrid | Arganda del Rey | | Total nitrogen; arsenic; chromium; nickel; zinc; halogenated organic compounds; phenols; TOC[d]; chlorides; fluorides; COD[e] |
| 18 | 3389 | 1987 | 2.f | Madrid | Arganda del Rey | TSP[c]; TOC[d] | total nitrogen; phosphorus; chromium; copper; nickel; zinc; TOC[d]; chlorides; cyanides; fluorides; COD[e] |
| 18 | 4195 | 1975 | 2.f | Madrid | Arganda del Rey | Carbon monoxide; carbon dioxide; NMVOC[g]; nitrogen oxides; chromium; mercury; tetrachloroethylene; chlorine; TSP[c]; TOC[d] | Total nitrogen; chromium; mercury; halogenated organic compounds; chlorides; phosphorus; TOC[d]; COD[e] |
| 18 | 6717 | 1987 | 5.f | Madrid | Arganda del Rey | Methane; carbon monoxide; carbon dioxide; nitrous oxide; nitrogen oxides; sulfur oxides; TSP[c] | Phosphorus; TOC[d] |
| 19 | 1651 | 1980 | 4.b | Madrid | Mejorada del Campo | Ammonia | Total nitrogen; TOC[d]; chlorides; COD[e]; halogenated organic compounds |
| 19 | 3507 | 1996 | 2.f | Madrid | Mejorada del Campo | | Total nitrogen; copper; zinc; halogenated organic compounds; phenols; TOC[d]; chlorides; fluorides; COD[e] |
| 19 | 5967 | 1979 | 2.f | Madrid | Mejorada del Campo | Ammonia; copper; nickel; lead; TOC[d]; chlorine; TSP[c]; manganese | Total nitrogen; phosphorus; copper; halogenated organic compounds; ethylbenzene; TOC[d]; xylenes; chlorides; COD[e] |
| 20 | 1662 | 1984 | 3.c | Madrid | Arganda del Rey | Carbon monoxide; carbon dioxide; nitrogen oxides; sulfur oxides; $PM_{10}$[h]; chromium; copper; mercury; nickel; lead; dioxins + furans; TSP[c]; manganese; vanadium | |
| 48 | 5437 | 1987 | 2.f | Madrid | Pinto | Carbon monoxide; nitrogen oxides; sulfur oxides; TOC[d]; TSP[c] | Total nitrogen; phosphorus; copper; zinc; halogenated organic compounds; chlorides |
| 48 | 7736 | 1963 | 2.c.iii | Madrid | Getafe | Carbon monoxide; carbon dioxide; nitrogen oxides; mercury; lead; zinc | Total nitrogen; zinc; TOC[d]; chlorides |
| 52 | 6553 | 1985 | 8.a | Madrid | Collado Villalba | Methane; carbon monoxide; carbon dioxide; nitrous oxide; ammonia; NMVOC[g]; nitrogen oxides; sulfur oxides; arsenic; cadmium; mercury; nickel; $PM_{10}$[h]; chromium; dioxins + furans | Total nitrogen; phosphorus; TOC[d]; chlorides; COD[e] |
| 52 | 6558 | 1960 | 2.c.i | Madrid | Collado Villalba | Carbon dioxide; ammonia; nitrogen oxides; TSP[c]; carbon monoxide; sulfur oxides; $PM_{10}$[h]; TOC[d] | Total nitrogen; zinc; TOC[d]; fluorides; COD[e]; phosphorus; halogenated organic compounds; chlorides; cyanides |
| 52 | 6729 | 1987 | 5.f | Madrid | Collado Villalba | Methane; carbon monoxide; carbon dioxide; nitrous oxide; nitrogen oxides; sulfur oxides; TSP[c] | Phosphorus; TOC[d] |

[a] Year of commencement of operations.

[b] 2.c.i, 2.e: production and processing of metals; 2.c.iii: galvanization; 2.f: surface treatment of metals and plastic; 3.c: cement and lime; 4.b: inorganic chemical industry; 5.a: hazardous waste; 5.e: disposal or recycling of animal waste; 5.f: urban waste-treatment treatment plants; 8.a: food and beverage sector; 9.c: surface treatment using organic solvents.

[c] Total suspended particulate matter.

[d] Total organic carbon.

[e] Chemical oxygen demand.

[f] Polycyclic aromatic hydrocarbons.

[g] Non-methane volatile organic compounds.

[h] Particulate matter with a diameter between 2.5 and 10 μm.

Figure S1: association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly, and for the sensitivity analysis with only women residing in their current residence for ≥2 years. Note that vertical axes are not in the same scale in the four graphics.

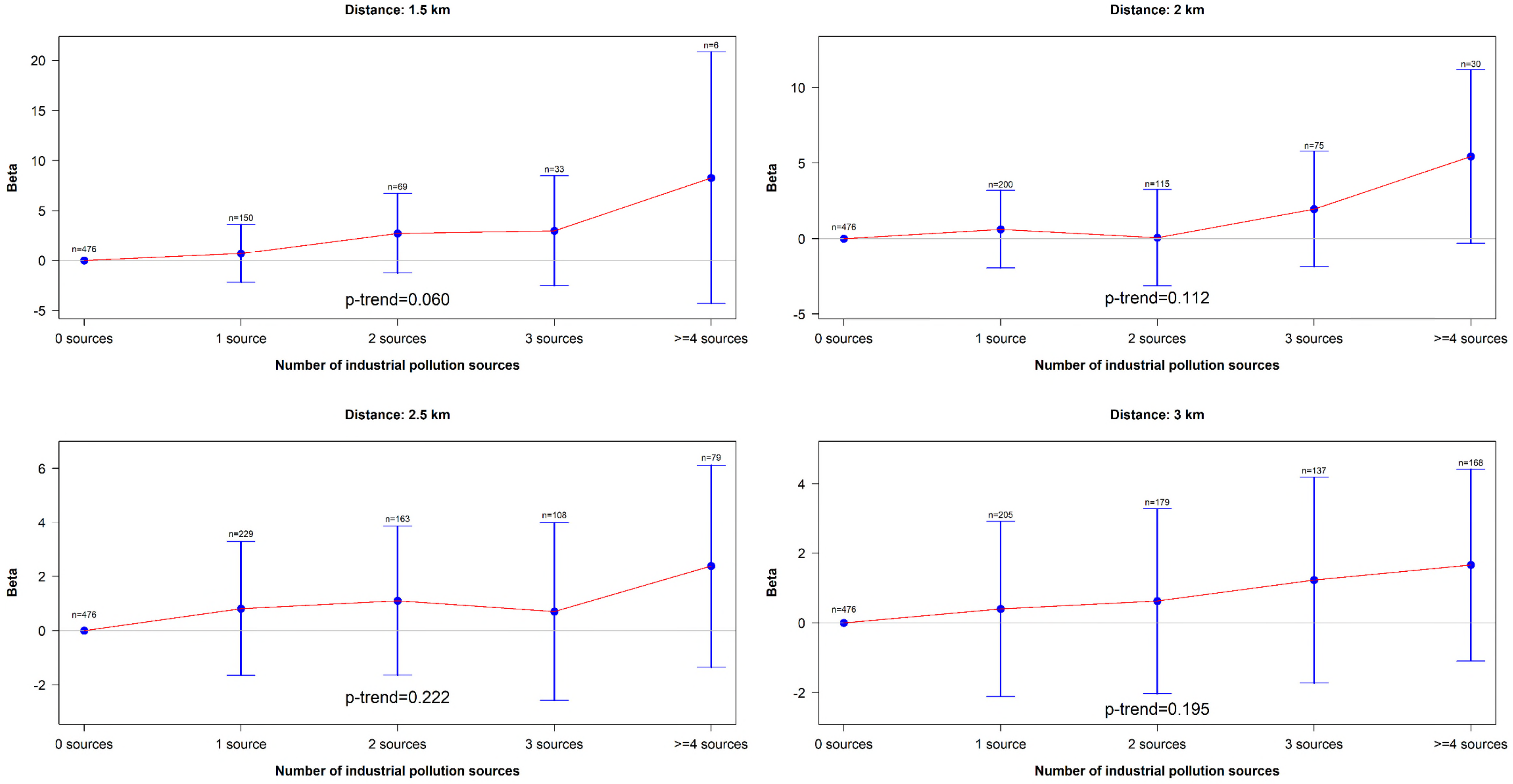


Figure S2: association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly, and for the sensitivity analysis with only women residing in their current residence for ≥10 years. Note that vertical axes are not in the same scale in the four graphics.