Occupational, dietary and other risk factors for myelodysplastic syndromes in Western Greece

[1,2]Christina Avgerinou, [1]Ioanna Giannezi*, [1]Stela Theodoropoulou*, [1]Vasileios Lazaris*, [1]Georgia Kolliopoulou*, [1]Vassiliki Labropoulou, [3]Panayiotis Zikos, [2]Yannis Alamanos, [2]Michail Leotsinidis, [1]Argiris Symeonidis

[1]Hematology Division, Department of Internal Medicine, Medical School, University of Patras, Greece

[2]Laboratory of Public Health, Medical School, University of Patras, Greece

[3]Department of Hematology, "St Andrew" General Hospital, Patras, Greece

* *equally contributed as co-authors*

Corresponding author:

Argiris Symeonidis

Phone: +302610999247

Fax: +302610993950

e-mail: argiris.symeonidis@yahoo.gr

Abstract

Purpose: We have observed an increasing incidence of myelodysplastic syndromes (MDS) in the geographic area of Western Greece during the past two decades. The objective of this study was to investigate potential risk factors for the manifestation of MDS in this area of Greece.

Methods: A hospital-based case-control study was conducted in the public hospitals of the region. Participants were interviewed based on a questionnaire regarding demographics, occupational exposures, smoking, alcohol consumption, dietary and domestic factors.

Results: A total of 228 individuals (126 cases, 102 controls) were recruited in this study. Univariate analysis showed that risk of MDS was associated with a family history of hematologic malignancy or solid tumor, exposure to pesticides, insecticides, herbicides, increased weekly intake of meat and eggs, and increased alcohol intake, whereas fruit intake had a protective effect. Analysis by pesticide ingredient showed a weak association of exposure to paraquat and glyphosate with the occurrence of MDS. Multivariate analysis showed that independent risk factors for the manifestation of MDS were family history of solid tumor (OR 2.47, 95% CI 1.32-4.65), meat intake for ≥ 5 days/week (OR 2.67, 95% CI 1.05-6.80) and exposure to pesticides (OR 3.25, 95% CI 1.73-6.11).

Conclusions: Exposure to pesticides is a major risk factor of MDS in Western Greece. Family history of solid tumor and increased meat intake also appear to play a role in the pathogenesis of MDS. Public health authorities should implement policies to advise and protect farmers from the harmful effects of agrochemicals. Emphasis should also be given to health promotion advice including healthy eating.

Key words:

Myelodysplastic syndromes

Risk factors

Pesticides

Glyphosate

Paraquat

Dietary factors

Stressful life event

Comorbidities

Introduction

The incidence of MDS increases with age and it varies significantly among different countries. Ageing carries an increased risk for different types of cancer, and it is well-recognized that previous chemotherapy or radiation therapy predispose to therapy-related MDS (t-MDS) [1]. Among other factors that have been studied, benzene and ionizing radiation have been clearly proven to be carcinogenic to the hematopoietic system [2]. Many other occupational exposures have been suspected to play a role, but most frequently data are insufficient for a definite conclusion. During the past years there has been an increasing interest in investigating the role of smoking, as well as the potential harm from the use of agricultural chemicals.

The administrative region of Western Greece consists of three prefectures: Achaia, Ilia and Etolia-Akarnania, and has a population of 679,796 inhabitants according to 2011 census. We have conducted a retrospective epidemiological study on the incidence of MDS in this region, during the period 1990-2009, which revealed an increasing trend for diagnosing an MDS. This was mainly attributed to an increase of RA and RARS, whereas the incidence of RAEB and CMML remained rather stable over the study period [3]. The observed increasing trend in the incidence of MDS in Western Greece led us to search for potential risk factors in this particular region. Therefore, the objective of the present study was to investigate the role of occupational, environmental, dietary and lifestyle factors in the pathogenesis of MDS in this geographic area.

Patients and methods

1. Study population

A hospital-based case-control study was conducted for the purposes of this research. The group of cases consisted of prevalent de novo MDS patients, who attended the Hematology outpatient clinic at the University Hospital of Patras and at "St Andrew" General Hospital of Patras in Western Greece. Only patients with a confirmed diagnosis of MDS, according to FAB classification [4] after bone marrow examination, were included in the study. Patients with a previous history of chemotherapy or radiation therapy were not included.

The group of controls consisted of patients admitted to the Ophthalmology Department of the University Hospital of Patras, to undergo elective operation for cataract. Patients with a history of hematological disorder and/or previous chemotherapy or radiotherapy were excluded from the group of controls. Proportional matching of cases and controls was performed by gender and age.

Both cases and controls were interviewed based on the same questionnaire. Interviews were conducted in hospital by medical doctors, between November 2009 and July 2013. The questionnaire included:

a) Demographic data, such as gender, age, area of residence, years of education, marital status and profession

b) Family history of hematologic malignancy or solid tumor in the first degree relatives

c) Agricultural activities, exposure to agricultural chemicals, i.e. pesticides, insecticides, herbicides, fertilizers, and frequency of exposure. As regularly exposed were considered those who were using agrochemicals regularly as part of their routine agricultural practice. Rarely exposed were those who did not make use of pesticides routinely but only occasionally or under special circumstances. Indirectly exposed were those who did not use agrochemicals themselves but had been working with somebody else using them. When the individual reported exposure to pesticides, they were asked to recall brand names of the products they had been exposed to.

d) Exposure to a list of occupational risk factors

e) Nutritional factors

f) Smoking and alcohol intake

g) Domestic factors

h) Leisure activities and hobbies, and

i) Exposure to ionizing radiation for diagnostic purposes.

All individuals gave their informed consent to participate in the study. The protocol was approved by the Scientific and Ethical Committees of the two participating hospitals.

2. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 22.0. T-test was used for the comparison of means and independent samples t-test for the comparison between groups. Pearson's chi-square test was used for the comparison of percentages among groups. Logistic regression was performed to assess the impact of different

variables on the risk for MDS, by calculating odds ratio (OR) and its 95% confidence intervals (95% CI). Univariate analysis was initially performed for each factor separately. Variables with a p value <0.10 as well as matching variables (age and gender) were finally included in the multivariate analysis (via forward conditional method). P<0.05 was considered to be statistically significant unless otherwise specified.

Results

1. Demographic data

Totally 228 subjects participated in the study (126 cases and 102 controls). Mean age at the time of interview and gender distribution were not significantly different between the two groups. Cases and controls did not differ significantly by years of education (reflecting socioeconomic status), residence in a rural or urban area or marital status. More than half of the individuals in both groups were farmers (66% of cases and 56% of the controls) (primary or secondary occupation) (Table 1).

2. Exposure to potential risk factors – Univariate analysis

2.1. Family history of cancer

Patients with MDS reported a family history of hematologic malignancy (OR 3.56, 95% CI 1.15-11.02) or solid tumor (OR 2.46, 95% CI 1.39-4.36) more often than controls (Table 2).

2.2. Occupational risk factors

Patients with MDS were more frequently exposed to pesticides, compared to controls (OR 2.47, 95% CI 1.44-4.24). In particular, they were more frequently exposed to insecticides (OR 3.34, 95% CI 1.62-6.90) and herbicides (OR 2.27, 95% CI 1.14-4.51), whereas exposure to fungicides was not significantly different between cases and controls. Patients were consequently stratified into three groups, according to the frequency of their general exposure to pesticides (never, rarely, regularly exposed). People who were rarely (N=23) or indirectly exposed (N=7) were grouped together in stratified univariate analysis. The association was statistically significant, both in the group of low frequency and in the group of high frequency. There was also weak evidence suggesting that use of fertilizers may be associated with MDS (Table 2). The

use of protective measures during application did not seem to modify the risk of MDS among the exposed (p=0.254).

Among the 228 individuals, it was possible to identify status of exposure to certain pesticides in 185 of them. After analyzing these qualitative data we managed to match reported brand names to a list of pesticide ingredients (Table 3). In certain cases the individuals could not recall the actual names, therefore analysis was restricted to the ones that were confirmed.

Analysis by name of pesticide was done only for those encountered more frequently. Exposure to paraquat dichloride (Gramoxone) was associated with MDS (OR 4.90, 95% CI 1.05-22.75). There was also weak evidence that exposure to glyphosate (Roundup) may be associated with MDS (OR=2.57, 95% CI 0.96-6.84) (Table 2).

All cases and controls were interviewed, regarding exposure to dyes, colors, glues, veneers, greases, oil, gasoline, heavy metals, plastics, welding fumes, wood processing, carbon, sulphuric acid, carbon tetrachloride, acetone, turpentine, textile industry, and other occupational risk factors, but none of them was found to differ significantly between the two groups. However, for the majority of the above occupational factors the number of exposed individuals was very low (Table 2). In particular, the OR of exposure to tar, liquid gas, asbestos, steel dust, dry cleaning fumes, methanol, ionizing radiation, and electromagnetic radiation could not be calculated because the number of exposed individuals was 0 in either group of cases or controls.

2.3. Dietary factors

Diagnosis of MDS was associated with the consumption of meat for ≥ 5 days a week (OR 3.20, 95% CI 1.39-7.41) and of >2 eggs per week (OR 2.09, 95% CI 1.08-4.05). There was also weak evidence suggesting that consumption of dairy products more often than 5 days a week may be associated with MDS (OR 1.65, 95% CI 0.92-2.97). On the other hand, consumption of fruit more often than 5 days a week had a protective effect (OR 0.56, 95% CI 0.31-0.99). Finally, no difference in the weekly consumption of vegetables, fish, legumes and coffee between cases and controls was observed (Table 4).

2.4. Smoking and alcohol consumption

In the present study, no significant association between smoking and risk of MDS was found, even when current and former smokers were grouped together as ever-smokers (Table 5).

Regarding alcohol consumption, it was shown that the risk of MDS for those consuming ≥ 15 drinks (alcohol equivalents) per week was 2-fold higher, in comparison to those who consumed 0-14 drinks per week (OR 2.06, 95% CI 1.13-4.11). There was not sufficient evidence to prove any association between MDS and the kind of drink that had been consumed (wine, beer or spirits). Further analysis of a possible interaction between smoking and alcohol consumption did not show any significant results. However, a joint effect of smoking with exposure to pesticides was observed (OR 2.89, 95% CI 1.35-6.22) (Table 6).

2.5. Domestic, environmental risk factors, leisure activities and stressful life events

The participants of the study were interviewed on hair dye use, type of residence, proximity of residence with petrol station, with a mobile antenna, use of microwave oven, cordless or mobile phone, and use of computer, but none of these factors was significantly different between cases and controls. We also studied the use of domestic insecticides, as well as hobbies (gardening, wood preservation, preservation of car or motorbike, amateur use of coloring), but no significant difference was shown between cases and controls. Individuals were also interviewed briefly on their experience of any stressful life events. The prevalence of stressful life events in general was not different between cases and controls. There was weak evidence of an increased risk of MDS in those who had experienced loss or severe illness of a child, and reduced risk in those who had lost their spouse (Table 7).

2.6. Exposure to ionizing radiation for diagnostic purposes

No difference was shown between cases and controls regarding exposure to X-rays, computerized tomography (CT) scan, scintigram, mammogram, angiography, barium swallow, barium enema and intravenous pyelogram (Table 7).

3. Multivariate analysis of risk factors for MDS

In the multivariate analysis we included the matching variables (gender and age), as well as all variables for which p value was <0.10 in the univariate analysis. Hence, the following parameters were included in the analysis: gender, age, family

history of hematologic malignancy, family history of solid tumor, exposure to pesticides, exposure to fertilizers, alcohol consumption, weekly consumption of meat, eggs, dairy products, fruit and vegetables. Types of agricultural chemicals (i.e. herbicides, insecticides) as well as the frequency of exposure were not included in the multivariate analysis, because they had already been taken into account by including general exposure to pesticides.

Multivariate analysis showed that the following three variables were independently associated with the risk of MDS: family history of solid tumor (OR 2.47, 95% CI 1.32-4.65), consumption of meat ≥ 5 days a week (OR 2.67, 95% CI 1.05-6.80), and exposure to pesticides (OR 3.25, 95% CI 1.73-6.11) (Table 8).

4. Myelodysplastic syndromes and comorbidities

Presence of other comorbid conditions was retrieved from medical records and confirmed during the interview. Such data were available for 200/228 participants (88%), and were missing for 11/126 cases (9%) and 17/102 controls (17%). Remarkably, history of osteoarthritis (OR 0.20, 95% CI 0.09-0.46), allergy (OR 0.20, 95% CI 0.08-0.54) and hypertension (OR 0.44, 95% CI 0.24-0.77) appeared to have a negative association with MDS (Table 9).

Discussion

The etiology of de novo MDS is unknown and probably multifactorial. This study attempted to investigate a wide spectrum of potential risk factors, most but not all of which had previously been reported in the literature.

Few studies have demonstrated an association of MDS with family history of hematologic malignancy [5,6] or other cancer [7]. In the present study we did find a significant association between MDS and family history of hematologic malignancy or solid tumor. Notably, the latter was confirmed as an independent risk factor in multivariate analysis. This finding implies the importance of genetic predisposition for cancer and deserves further investigation in large epidemiological studies.

Whereas cases and controls were similarly involved in farming and other agricultural activities, exposure to pesticides (and particularly herbicides and insecticides) was significantly associated with MDS, and this proved to be an independent risk factor in multivariate analysis. Exposure to agricultural chemicals has been studied extensively as a risk factor, and most studies indicate a positive

association with MDS [6,7,8,9,10,11,12], although in some others, no significant association was found [13,14]. A recent meta-analysis of 11 case-control studies confirmed a significant association between MDS and exposure to pesticides. Increased risk was also associated with exposure to insecticides, but not to herbicides or fungicides [15]. In another meta-analysis, exposure to pesticides was associated with the manifestation of other hematologic malignancies, and, in a stratified analysis, association was only found with non-Hodgkin lymphoma (NHL), whereas results for leukemia and multiple myeloma were borderline significant [16]. In addition, another meta-analysis has also shown a significant association between occupational exposure to pesticides and myeloid leukemia [17]. Apart from hematologic malignancies, exposure to pesticides has been associated with solid tumors, such as brain, breast, pancreatic, prostate, and stomach cancer [18].

Among types of pesticides associated with carcinogenesis are the following [19]:

1. Organochlorine insecticides, such as:

a) DDT (4,4'-Dichlorodiphenyltrichloroethane): classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic (Class 2B) since 1991 but recently upgraded to Class 2A (probably carcinogenic) [20,21].
b) Chlordane: classified as Class 2B (possibly carcinogenic) [20].
c) Lindane: recently reviewed by IARC and upgraded from Class 2B (possibly carcinogenic) to Class 1 (carcinogenic) [21], linked specifically to NHL [22].

2. Organophosphate insecticides: such as Dichlorvos (DDVP), classified as Class 2B (possibly carcinogenic) [20].
3. Herbicides such as 2,4-D (2,4-dichlorophenoxyacetic acid), recently classified as possibly carcinogenic (class 2B) [21], and glyphosate (isopropylamine salt): recently classified by IARC as Class 2A (probably carcinogenic) [20].

In our study we found an increased risk of MDS in subjects exposed to glyphosate, although not statistically significant. We also found an association of MDS with exposure to paraquat. A prospective cohort in the US reported an association between exposure to paraquat and NHL, as well as a non-significantly elevated relative risk for leukemia [23].

Occupational exposure to many other risk factors has been previously investigated, and MDS has been associated with exposure to radiation, organic substances, metals (copper) and hydrogen peroxide [13], exposure to organic solvents [5,6,24], petroleum and textile dust [5]. In the present study the participants were

interviewed on history of exposure to potential occupational risks, but no significant association with MDS was observed. However, the total number of exposed persons was really low in the studied population, and it might not have been possible to reveal such an association even if it really existed. This is mainly explained by the fact that Western Greece is a rather agricultural than industrial region.

The role of diet in MDS is still obscure. In our study cases consumed meat and eggs more often than controls, and controls consumed fruit more often than cases. Among these, only consumption of meat for ≥5 days a week proved to be an independent risk factor in multivariate analysis. A large cohort study revealed obesity as a risk factor for MDS, whereas participation in vigorous physical activity had a protective role. In the same cohort, no association was found between MDS and meat, fruit or vegetable intake [25]. Another study found a positive association of MDS with coffee intake [7], whereas coffee intake was not different between cases and controls in our study. A case-control study conducted in China showed that tea consumption has a protective role against MDS [26].

In the present study, no significant association was revealed between smoking and MDS. Smoking has been studied thoroughly as a risk factor for myelodysplasia in many studies. Most of them revealed a significant association of smoking with MDS [9,25,28,29,30], whereas others did not [8,13,27]. A meta-analysis confirmed that smoking plays an important role in the occurrence of MDS [32]. Finally, another study showed that alcohol intake and smoking jointly increased the risk of MDS, whereas each of these factors alone had limited effect [33]. In our study there was weak evidence that the effect of smoking was enhanced by drinking alcohol, even though the result was not significant. Nevertheless, we found that the combination of smoking and exposure to pesticides increased the risk for MDS. This joint effect has been reported by Strom et al [6]. In a case-control study conducted in Thessaly, central Greece, it was shown that smoking during pesticide application increased the risk of MDS and other hematologic malignancies [12].

Smoking is considered to be the main non-occupational source of exposure to benzene, which is longtime known for its leukemogenic effect in humans [34,35]. A number of studies have investigated the impact of smoking on the cytogenetics of patients with MDS, and some of them have found a positive association between smoking and abnormal karyotype [6,36]. Abnormal karyotype has also been investigated in relation to occupational exposure in some studies [36,37,38].

In the present study the consumption of ≥15 drinks-alcohol equivalents per week was associated with increased risk of MDS. Alcohol consumption has been addressed as a risk factor for MDS, with some studies showing a positive association [7,27] and some others not [31].

Hair dye use has been reported to be associated with a significantly increased risk of MDS in some [9,24] but not all [37] studies, but no association was confirmed in our study. Among the leisure activities studied, none was found to be associated with an increased risk of MDS. West et al studied the role of ionizing radiation for diagnostic purposes and found that exposure to dental X-rays and possibly bone X-rays was associated with MDS [13]. On the contrary, Nisse et al did not find such an association [5]. In our study we did not find a significant impact of the number of radiology investigations, however the sample was small and this question is probably subject to recall bias.

To our knowledge, the role of stressful life events in MDS has not been explored. Stressful life events have been linked with other types of cancer (e.g. breast cancer [39]). Stress can affect different pathways of the immune system [40]. In our study we did not find an overall difference in reported stressful life events between cases and controls. However, cases had more frequently suffered loss or severe illness of their child, whereas controls had experienced more often death of their spouse. A study with a larger number of participants and more detailed interrogation on perceived stress could probably shed more light on this unexplored aspect of MDS pathogenesis.

Finally, multivariate analysis showed that exposure to pesticides, increased meat intake and family history of cancer were independent risk factors for MDS in Western Greece.

Despite the small number of participants, we attempted to compare comorbidities between cases and controls. We found a higher prevalence of hypertension, allergy and osteoarthritis in the group of controls. Few studies have studied the association of MDS with other diseases. Dalamaga et al found an association between MDS and autoimmune thyroid disease [41], and another study with data from the General Practice Research Database showed a slightly increased risk of MDS in patients diagnosed with any autoimmune disorder more than 10 years before diagnosis of MDS [42]. MDS have also been associated with other comorbid conditions, such as Crohn's disease [43], Helicobacter pylori infection [44] and HIV infection [45,46].

The limitations of the present study are mainly related to its nature. As a case-control study, information was collected retrospectively and there may be a recall bias, as many exposures happened decades before. One methodological pitfall in similar studies is that MDS patients may try harder than controls to attribute their disease to some factors, thus increasing the recorded exposure rate in the group of cases. Additionally, the interviewer was not blinded as to the case/control status of the participants. The number of participants was relatively small. A larger number of participants would increase statistical power and it might have allowed more associations to be revealed. Prevalent (not incident) cases of MDS were recruited and some of the conditions may have slightly changed since the date of diagnosis. For instance, the nutrition of patients with MDS may have been modified due to anemia or other laboratory findings, and the answers given may not reflect their dietary habits before diagnosis. Finally, information was obtained in a face-to-face interview and not by a self-administered questionnaire. Therefore, it is not known whether the participants replied honestly, especially regarding alcohol consumption or stressful life events. However, the present study could not have been realized otherwise, given that patients were elderly and more than half of them had only primary education.

All of the above underline the complexity of mechanisms involved, and imply that the pathogenesis of MDS is multifactorial. Given the increasing bulk of evidence, it is mandatory to minimize occupational and environmental exposure to agrochemicals. Public health authorities should implement policies in order to advise and protect farmers from the harmful effects of exposure to pesticides. Emphasis should be given on health promotion, smoking cessation, maintaining a healthy diet and psychological well-being.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgements

First of all, we are grateful to Dr Robert West, Emeritus Professor of Epidemiology at the University of Cardiff, UK, who sent us the questionnaires he and his colleagues had created for the research of risk factors for MDS. We eventually created our own questionnaire, adjusted to the features of the Greek population, but Dr West gave us an

idea of the full list of risk factors that had been studied by his team. We are also grateful to Dr Nikolaos Pharmakakis, Professor of Ophthalmology at the University of Patras, and Dr Sotirios Gartaganis, Emeritus Professor of Ophthalmology at the University of Patras, who collaborated with us on the constitution of the control group from the Department of Ophthalmology, University Hospital of Patras, Greece. We also want to thank all the doctors and nurses from the same department who facilitated the procedure of the interviews. We are grateful to all the doctors from the Division of Hematology, Department of Internal Medicine, University of Patras, and especially to Dr Alexandra Kouraklis, Dr Polyxeni Lampropoulou, Dr Maria Tiniakou, Dr Tzouvara Evangelia, Dr Fragopanagou Eleni, and Dr Marina Karakantza, Associate Professor of Hematology. We would like to thank the staff from the same department, and especially Nurse Mrs Evgenia Vretou and Laboratory technician Mrs Maria Kontogeorgi for their assistance at the Hematology outpatient clinic. We are finally grateful to the patients with MDS and to the patients from the Department of Ophthalmology, who gave their consent to participate in the study.

References

1. Levine EG, Bloomfield CD. Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin Oncol 1992; 19(1):47-84.

2. Descatha A, Jenabian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: overview on human recent data. Cancer Causes Control 2005; 16(8):939-953.

3. Avgerinou C, Alamanos Y, Zikos P, Lampropoulou P, Melachrinou M, Labropoulou V, Tavernarakis I, Aktypi A, Kaiafas P, Raptis C, Kouraklis A, Karakantza M, Symeonidis A. The incidence of myelodysplastic syndromes in Western Greece is increasing. Ann Hematol 2013 Jul; 92(7):877-87.

4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C. French-American-British (FAB) Co-operative Group. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982; 51(2):189-199.

5. Nisse C, Haguenoer JM, Grandbastien B, Preudhomme C, Fontaine B, Brillet JM, Lejeune R, Fenaux P. Occupational and environmental risk factors of the myelodysplastic syndromes in the North of France. Br J Haematol 2001; 112(4):927-935.

6. Strom SS, Gu Y, Gruschkus SK, Pierce SA, Estey EH. Risk factors for myelodysplastic syndromes: a case-control study. Leukemia 2005; 19(11):1912-1918.

7. Pekmezovic T, Suvajdzic Vukovic N, Kisic D, Grgurevic A, Bogdanovic A, Gotic M, Bakrac M, Brkic N. A case-control study of myelodysplastic syndromes in Belgrade (Serbia Montenegro). Ann Hematol 2006; 85(8):514-519.

8. Ciccone G, Mirabelli D, Levis A, Gavarotti P, Rege-Cambrin G, Davico L, Vineis P. Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study. Cancer Genet Cytogenet 1993; 68(2):135-139.

9. Lv L, Lin G, Gao X, Wu C, Dai J, Yang Y, Zou H, Sun H, Gu M, Chen X, Fu H, Bao L. Case-control study of risk factors of myelodysplastic syndromes according to World Health Organization classification in a Chinese population. Am J Hematol 2011; 86(2):163-169.

10. Rigolin GM, Cuneo A, Roberti MG, Bardi A, Bigoni R, Piva N, Minotto C, Agostini P, De Angeli C, Del Senno L. Exposure to myelotoxic agents and myelodysplasia: case-control study and correlation with clinicobiological findings. Br J Haematol 1998; 103(1):189-197.

11. Goldberg H, Lusk E, Moore J, Nowell PC, Besa EC. Survey of exposure to genotoxic agents in primary myelodysplastic syndrome: correlation with chromosome patterns and data on patients without hematological disease. Cancer Res 1990; 50(21):6876-6881.

12. Kokouva M, Bitsolas N, Hadjigeorgiou GM, Rachiotis G, Papadoulis N, Hadjichristodoulou C. Pesticide exposure and lymphohaematopoietic cancers: a case-control study in an agricultural region (Larissa, Thessaly, Greece). BMC Public Health 2011 Jan 4; 11:5.

13. West RR, Stafford DA, Farrow A, Jacobs A. Occupational and environmental exposures and myelodysplasia: a case-control study. Leuk Res 1995; 19(2):127-139.

14. Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, Burmeister LF, Van Lier SF, Dick F. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res 1990; 50(20):6585-6591.

15. Jin J, Yu M, Hu C, Ye L, Xie L, Jin J, Chen F, Tong H. Pesticide exposure as a risk factor for myelodysplastic syndromes: a meta-analysis based on 1,942 cases and 5,359 controls. PLoS One 2014; 9(10):e110850.

16. Merchi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. Cancer Causes Control 2007; 18(10):1209-1226.

17. Van Maele-Fabry G, Duhayon S, Lison D. A systematic review of myeloid leukemias and occupational pesticide exposure. Cancer Causes Control 2007; 18(5):457-478.

18. Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides. Can Fam Physician 2007; 53(10):1704-1711.

19. Alavanja MC, Bonner M. Pesticides and human cancers. Cancer Invest 2005; 23(8):700-711.

20. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. List of classifications, volumes 1-113. (last update 26 June 2015) (http://monographs.iarc.fr/ENG/Classification/)

21. Loomis D, Guyton K, Grosse Y, El Ghissassi F, Bouvard V, Bendrahim-Tallaa L, Guha N, Heidi Mattock, Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France. Lancet Oncol 2015; 16:891-892.

22. Alavanja MCR, Hofmann JN, Lynch CF, Hines CJ, Barry KH, et al. Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. PLoS One 2014; 9(10):e109332.

23. Park SK, Kang D, Beane-Freeman L, Gwak J, Hoppin JA, Sandler DP, Knott C, Lynch CF, Blair A, Alavanja M. Cancer incidence among paraquat exposed pesticide applicators in the Agricultural Health Study. Int J Occup Environ Health 2009; 15(3):274-281.

24. Nagata C, Shimizu H, Hirashima K, Kakishita E, Fujimura K, Niho Y, Karasawa M, Oguma S, Yoshida Y, Mizoguchi H. Hair dye use and occupational exposure to

organic solvents as risk factors for myelodysplastic syndromes. Leuk Res 1999; 23(1):57-62.

25. Ma X, Lim U, Park Y, Mayne ST, Wang R, Hartge P, Hollenbeck AR, Schatzkin A. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. Am J Epidemiol 2009; 169(12):1492-1499.

26. Liu P, Zhang M, Jin J, Holman CD. Tea consumption reduces the risk of de novo myelodysplastic syndromes. Leuk Res 2015; 39(2):164-169.

27. Ido M, Nagata C, Kawakami N, Shimizu H, Yoshida Y, Nomura T, Mizoguchi H. A case-control study of myelodysplastic syndromes among Japanese men and women. Leuk Res 1996; 20(9):727-731.

28. Pasqualetti P, Festuccia V, Acitelli P, Collaciani A, Giusti A, Casale R. Tobacco smoking and risk of hematologic malignancies in adults: a case-control study. Br J Haematol 1997; 97(3):659-662.

29. Björk J, Albin M, Mauritzson N, Strömberg U, Bertil J, Hagmar L. Smoking and myelodysplastic syndromes. Epidemiology 2000; 11(3):285-291.

30. Björk J, Johansson B, Broberg K, Albin M. Smoking as a risk factor for myelodysplastic syndromes and acute myeloid leukemia and its relation to cytogenetic findings: A case-control study. Leuk Res 2009; 33(6):788-791.

31. Du Y, Fryzek J, Sekeres M, Taioli E. Smoking and alcohol intake as risk factors for myelodysplastic syndromes (MDS). Leuk Res 2009; 34(1):1-5.

32. Tong H, Hu C, Yin X, Yu M, Yang J, Jin J. A meta-analysis of the relationship between cigarette smoking and incidence of myelodysplastic syndromes. PLoS One 2013; 8(6):e67537.

33. Dalamaga M, Petridou E, Cook FE, Trichopoulos D. Risk factors for myelodysplastic syndromes: a case-control study in Greece. Cancer Causes Control 2002; 13(7):603-608.

34. Aksoy M, Ozeris S, Sabuncu H, Inanici Y, Yanardag R. Exposure to benzene in Turkey between 1983 and 1985: a haematological study on 231 workers. Br J Ind Med 1987; 44(11):785-787.

35. Smith MT, Zhang L, McHale CM, Skibola CF, Rappaport SM. Benzene, the exposome and future investigations of leukemia etiology. Chemico-Biological Interactions 2011; 192(1-2):155-159.

36. Davico L, Sacerdote C, Ciccone G, Pegoraro L, Kerim S, Ponzio G, Vineis P. Chromosome 8, occupational exposures, smoking, and acute nonlymphocytic leukemias: a population-based study. Cancer Epidemiol Biomarkers Prev 1998; 7(12):1123-1125.

37. Albin M, Björk J, Welinder H, Tinnerberg H, Mauritzson N, Billstrom R, Strömberg U, Mikoczy Z, Johansson B, Ahlgren T, Nilsson PG, Mitelman F, Hagmar L. Cytogenetic and morphologic subgroups of myelodysplastic syndromes in relation to occupational and hobby exposures. Scand J Work Environ Health 2003; 29(5):378-387.

38. West RR, Stafford DA, White AD, Bowen DT, Padua RA. Cytogenetic abnormalities in the myelodysplastic syndromes and occupational or environmental exposure. Blood 2000; 95(6):2093-2097.

39. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M. Stressful life events and risk of breast cancer in 10,808 women: a cohort study. Am J Epidemiol 2003; 157(5):415-423.

40. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 2004; 130(4):601-630.

41. Dalamaga M, Lekka A, Karmaniolas K, Stathopoulou E, Dionyssiou-Asteriou A. Is thyroid autoimmunity a risk factor for developing primary myelodysplastic syndrome? Cancer Causes Control 2008; 19(4):371-378.

42. Wilson AB, Neogi T, Prout M, Jick S. Relative risk of myelodysplastic syndromes in patients with autoimmune disorders in the General Practice Research Database. Cancer Epidemiol 2014; 38(5):544-549.

43. Bosch X, Bernadich O, Manel V. The association between Crohn disease and the myelodysplastic syndromes: report of 3 cases and review of the literature. Medicine (Baltimore) 1998; 77(6):371-377.

44. Diamantidis MD, Ioannidou-Papagiannaki E, Kountouras J, Mandala E, Tsapournas G, Frida-Michailidou I, Klonizakis P, Zavos C, Haralambidou-Vranitsa S, Vlachaki E, Parapanisiou E, Klonizakis I. High prevalence of Helicobacter pylori infection in Greek patients with myelodysplastic syndromes. Acta Haematol 2010; 124(3):141-149.

45. Rieg S, Lübbert M, Kern WV, Timme S, Gärtner F, Rump J-A. Myelodysplastic syndrome with complex karyotype associated with long-term highly active antiretroviral therapy. Br J Haematol 2009; 145(5):670-673.

46. Takahashi K, Yabe M, Shapira I, Pierce S, Garcia-Manero G, Varma M. Clinical and cytogenetic characteristics of myelodysplastic syndromes in patients with HIV infection. Leuk Res 2012; 36(11):1376-1379.

Table 1. Demographics of cases and controls.

Variable	Group	N	Controls	Cases	p value
Gender	**Men**	159	69	90	0.537 (ns)
	Women	69	33	36	
Area of residence	**Rural**	125	54	71	0.607 (ns)
	Urban	103	48	55	
Years of education	**0**	14	7	7	0.985 (ns)
	1-6	127	57	70	
	7-9	31	13	18	
	10-12	27	13	14	
	>12	26	12	14	
	Unknown	3	0	3	
Marital status	**Married**	173	81	92	0.505 (ns)
	Single	8	2	6	
	Divorced	4	1	3	
	Widower	43	18	25	
Profession	**Farmer (1st occupation)**	92	31	61	
	Farmer (2nd occupation)	48	26	22	
	Farmers (total)	140	57	83	0.123 (ns)
	Non-farmers	88	45	43	
Mean age (standard deviation) [range]			75.3 (6.69) [56-88]	75.2 (7.98) [53-93]	0.915 (ns)
Total			**102**	**126**	

Table 2. Family history of hematologic and other malignancy and exposure to occupational risk factors (univariate analysis).

Variable	Category	N	Controls	Cases	OR	95% CI	p value
Family history of hematologic malignancy	**No**	208	98	110	1.00	(Ref.)	**0.027**
	Yes	20	4	16	3.56	1.15-11.02	
Family history of solid tumor	**No**	147	77	70	1.00	(Ref.)	**0.002**
	Yes	81	25	56	2.46	1.39-4.36	
Agricultural activities	**No**	71	36	35	1.00	(Ref.)	0.224 (ns)
	Yes	157	66	91	1.42	0.81-2.49	
Pesticides	**No**	122	67	55	1.00	(Ref.)	**0.001**
	Yes	106	35	71	2.47	1.44-4.24	
Frequency of exposure to pesticides	**Never**	122	67	55	1.00	(Ref.)	**0.005**
	Rarely/Indirectly	30	10	20	2.44	1.05-5.64	
	Regularly	76	25	51	2.48	1.37-4.51	
Fungicides	**No**	172	75	97	1.00	(Ref.)	0.541 (ns)
	Yes	26	13	13	0.77	0.34-1.77	
Insecticides	**No**	148	76	72	1.00	(Ref.)	**0.001**
	Yes	50	12	38	3.34	1.62-6.90	
Herbicides	**No**	148	73	75	1.00	(Ref.)	**0.019**
	Yes	50	15	35	2.27	1.14-4.51	
Fertilizers	**No**	152	72	80	1.00	(Ref.)	**0.073**
	Yes	49	16	33	1.86	0.94-3.65	
Glyphosate	**No**	162	77	86	1.00	(Ref.)	**0.060**
	Yes	23	6	17	2.57	0.96-6.84	
Paraquat	**No**	172	81	91	1,00	(Ref.)	**0.043**
	Yes	13	2	11	4.90	1.05-22.75	
Propineb	**No**	171	74	97	1.00	(Ref.)	0.138 (ns)
	Yes	14	9	5	0.42	0.14-1.32	
Deltamethrin	**No**	176	80	96	1.00	(Ref.)	0.480 (ns)
	Yes	9	3	6	1.67	0.40-6.88	
Colors	**No**	202	93	109	1.00	(Ref.)	0.273 (ns)
	Yes	26	9	17	1.61	0.69-3.79	
Dyes	**No**	203	94	109	1.00	(Ref.)	0.180 (ns)
	Yes	25	8	17	1.83	0.76-4.44	

Veneers	**No**	213	95	118	1.00	(Ref.)	0.876 (ns)
	Yes	15	7	8	0.92	0.32-2.63	
Glues	**No**	219	99	120	1.00	(Ref.)	0.487 (ns)
	Yes	9	3	6	1.65	0.40-6.77	
Gasoline	**No**	198	91	107	1.00	(Ref.)	0.342 (ns)
	Yes	30	11	19	1.47	0.66-3.25	
Oil	**No**	205	90	115	1.00	(Ref.)	0.451 (ns)
	Yes	23	12	11	0.72	0.30-1.70	
Greases	**No**	204	89	115	1.00	(Ref.)	0.329 (ns)
	Yes	24	13	11	0.65	0.28-1.53	
Heavy metals	**No**	221	98	123	1.00	(Ref.)	0.507 (ns)
	Yes	7	4	3	0.60	0.13-2.73	
Plastics	**No**	221	99	122	1.00	(Ref.)	0.919 (ns)
	Yes	7	3	4	1.08	0.24-4.95	
Welding fumes	**No**	225	101	124	1.00	(Ref.)	0.692 (ns)
	Yes	3	1	2	1.56	0.15-18.22	
Wood processing	**No**	226	99	123	1.00	(Ref.)	0.793 (ns)
	Yes	6	3	3	0.77	0.16-4.07	
Carbon	**No**	226	101	125	1.00	(Ref.)	0.881 (ns)
	Yes	2	1	1	0.81	0.05-13.08	
Sulphuric acid	**No**	225	101	124	1.00	(Ref.)	0.692 (ns)
	Yes	3	1	2	1.63	0.15-18.22	
Carbon tetrachloride	**No**	226	101	125	1.00	(Ref.)	0.881 (ns)
	Yes	2	1	1	0.81	0.05-13.08	
Acetone	**No**	225	101	124	1.00	(Ref.)	0.692 (ns)
	Yes	3	1	2	1.63	0.15-18.22	
Turpentine	**No**	224	101	123	1.00	(Ref.)	0.438 (ns)
	Yes	4	1	3	2.46	0.25-24.05	
Textile industry	**No**	222	98	124	1.00	(Ref.)	0.289 (ns)
	Yes	6	4	2	0.39	0.07-2.20	

Table 3. Pesticide ingredients and number of individuals who reported a specific exposure in our study.

Ingredient	IARC classification	N
Herbicides		
Glyphosate	Group 2A	23
Paraquat	not listed	13
Fluazifop-P-butyl	not listed	1
Simazine	Group 3	1
Propanil	not listed	2
Insecticides		
0.05% Pyrethrins, 0.4% Permethrin, 0.1% Pyripoxyfen	Permethrin classified in Group 3 (other ingredients not listed)	5
Deltamethrine	Group 3	9
DDT (dichlorodiphenyltrichloroethane)	Group 2A	2
Methamidophos	not listed	4
Endosulfan	Group 2A	1
Demeton-O + demeton-S, mercaptophos	not listed	2
Methamidophos	not listed	1
Sodium arsenate	Group 1	2
Morphothion (organophosphate)	not listed	3
Dimethoate (organophosphate)	not listed	2
Fenthion (organophosphate)	not listed	1
Malathion (organophosphate)	Group 2A	1
Carbofuran (carbamate)	not listed	1
Methomyl (carbamate)	not listed	1
Lindane (organochlorine)	1	1
Aldrin (organochlorine)	3	1
Fungicides		
Propineb	not listed	14
Metalaxyl-M, mancozeb	not listed	5

IARC Classification groups

Group 1 *Carcinogenic to humans*

Group 2A *Probably carcinogenic to humans*

Group 2B *Possibly carcinogenic to humans*

Group 3 *Not classifiable as to its carcinogenicity to humans*

Group 4 *Probably not carcinogenic to humans*

Table 4. Nutritional factors (univariate analysis).

Food	Frequency	N	Controls	Cases	OR	95% CI	p value
Meat	**0-4 days/week**	**193**	94	99	1.00	(Ref.)	**0.006**
	5-7 days/week	**35**	8	27	3.20	1.39-7.41	
Eggs	**0-2 /week**	**176**	86	90	1.00	(Ref.)	**0.029**
	3-7 /week	**51**	16	35	2.09	1.08-4.05	
Dairy products	**0-5 days /week**	**63**	34	29	1.00	(Ref.)	**0.091**
	6-7 days /week	**164**	68	96	1.65	0.92-2.97	
Fruit	**0-5 days /week**	**71**	25	46	1.00	(Ref.)	**0.048**
	6-7 days /week	**156**	77	79	0.56	0.31-0.99	
Vegetables	**0-5 days /week**	**94**	37	57	1.00	(Ref.)	0.157 (ns)
	6-7 days /week	**133**	65	68	0.68	0.40-1.16	
Fish	**0-2 days /week**	**194**	90	104	1.00	(Ref.)	0.287 (ns)
	3-7 days /week	**33**	12	21	1.51	0.71-3.25	
Legumes	**0-1 days /week**	**163**	70	93	1.00	(Ref.)	0.389 (ns)
	≥ 2 days /week	**65**	32	33	0.78	0.44-1.38	
Coffee	**0-1 /day**	**134**	57	77	1.00	(Ref.)	0.425 (ns)
	≥ 2 /day	**94**	45	49	0.81	0.47-1.37	

Table 5. Smoking and alcohol consumption (univariate analysis).

Variable	Category	N	Controls	Cases	OR	95% CI	p value
Smoking (1)	**Never**	**91**	43	48	1.00	(Ref.)	0.521 (ns)
	Current smokers	**45**	22	23	0.94	0.46-1.91	
	Ex-smokers	**92**	37	55	1.33	0.74-2.39	
Smoking (2)	**Never**	**91**	43	48	1.00	(Ref.)	0.534 (ns)
	Ever-smokers	**137**	59	78	1.18	0.69-2.02	
Alcohol use	**0-14 drinks/week**	**173**	85	88	1.00	(Ref.)	**0.019**
	≥ 15 drinks/week	**55**	17	38	2.06	1.13-4.11	
Wine	**No**	**58**	27	31	1.00	(Ref.)	0.748 (ns)
	Yes	**170**	75	95	1.10	0.61-2.01	
Beer	**No**	**184**	81	103	1.00	(Ref.)	0.657 (ns)
	Yes	**44**	21	23	0.86	0.44-1.66	
Spirits	**No**	**164**	72	92	1.00	(Ref.)	0.685 (ns)
	Yes	**64**	30	34	0.89	0.50-1.58	
Kind of drink	**No alcohol**	**47**	20	27	1.00	(Ref.)	0.914 (ns)
	Wine only	**94**	42	52	0.92	0.45-1.86	
	Beer only	**3**	2	1	0.37	0.03-4.37	
	Spirits only	**6**	4	2	0.37	0.06-2.22	
	Wine + beer	**20**	8	12	1.11	0.38-3.22	
	Wine + spirits	**37**	15	22	1.09	0.45-2.60	
	Beer + spirits	**2**	1	1	0.74	0.09-12.57	
	Wine + beer + spirits	**19**	10	9	0.67	0.23-1.94	

Table 6. Exploring the joint effect smoking/alcohol consumption and smoking/pesticide exposure (univariate analysis).

Variable	Category	N	Controls	Cases	OR	95% CI	p value
Smoking and alcohol use	**Never-smoker and no alcohol**	**29**	14	15	1.00	(Ref.)	0.093 (ns)
	Never-smoker and 1-14 drinks per week	**51**	27	24	0.83	0.33-2.07	
	Never smoker and ≥ 15 drinks per week	**11**	2	9	4.20	0.77-22.91	
	Ever-smoker and no alcohol	**15**	4	11	2.57	0.66-9.96	
	Ever-smoker and 1-14 drinks per week	**78**	40	38	0.88	0.38-2.08	
	Ever smoker and ≥ 15 drinks per week	**44**	15	29	1.80	0.69-4.71	
Smoking and pesticide exposure	**Never smoker and not exposed to pesticides**	**50**	29	21	1.00	(Ref.)	**0.011**
	Never smoker and exposed to pesticides	**41**	14	27	2.66	1.13-6.27	
	Ever-smoker and not exposed to pesticides	**72**	38	34	1.24	0.60-2.56	
	Ever-smoker and exposed to pesticides	**65**	21	44	2.89	1.35-6.22	

Table 7. Domestic and environmental factors and exposure to diagnostic procedures (univariate analysis).

Variable	Frequency	N	Controls	Cases	OR	95% CI	p value
Hair dye	**No**	198	86	112	1.00	(Ref.)	0.312 (ns)
	Yes	30	16	40	0.67	0.31-1.45	
Type of residence	**House**	184	79	105	1.00	(Ref.)	0.187 (ns)
	Block of flats	42	22	20	0.68	0.35-1.34	
Proximity of residence to petrol station	**No**	202	93	109	1.00	(Ref.)	0.187 (ns)
	Yes	25	8	17	1.81	0.75-4.39	
Proximity of residence to mobile antenna	**No**	213	97	116	1.00	(Ref.)	0.225 (ns)
	Yes	14	4	10	2.09	0.64-6.87	
Microwave oven	**No**	179	79	100	1.00	(Ref.)	0.833 (ns)
	Yes	48	22	26	0.93	0.49-1.77	
Cordless phone	**No**	125	63	62	1.00	(Ref.)	0.304 (ns)
	Yes	68	29	39	1.37	0.75-2.48	
Mobile phone	**No**	122	51	71	1.00	(Ref.)	0.340 (ns)
	Yes	106	51	55	0.77	0.46-1.31	
Use of computer	**No**	220	100	120	1.00	(Ref.)	0.386 (ns)
	Yes	7	2	5	2.03	0.40-10.97	
Domestic insecticides	**No**	101	49	52	1.00	(Ref.)	0.275 (ns)
	Yes	126	52	74	1.34	0.79-2.27	
Gardening	**No**	105	52	53	1.00	(Ref.)	0.395 (ns)
	Rarely	33	14	19	1.33	0.60-2.93	
	Often (≥1 weekly)	90	36	54	1.47	0.83-2.60	
Hobby related with dyes/coloring	**No**	206	92	114	1.00	(Ref.)	0.943 (ns)
	Yes	22	10	12	0.97	0.40-2.34	
Wood preservation	**No**	216	96	120	1.00	(Ref.)	0.707 (ns)
	Yes	12	6	6	0.80	0.25-2.56	
Preservation of car/motor bike	**No**	216	96	119	1.00	(Ref.)	0.916 (ns)
	Yes	13	6	7	0.94	0.31-2.89	
Stressful event	**No**	134	57	77	1.00	(Ref.)	0.384 (ns)
	Yes	93	45	48	0.79	0.46-1.34	

Type of stressful event	**None**	133	57	76	1.00	(Ref.)	**0.013**
	Death/severe illness of child	25	7	18	1.93	0.75-4.93	
	Death of spouse	31	22	9	0.31	0.13-0.72	
	Other	38	16	22	1.03	0.50-2.14	
X-rays	**0-9**	125	56	69	1.00	(Ref.)	0.978 (ns)
	10-19	54	25	29	0.94	0.50-1.79	
	≥ 20	45	20	25	1.01	0.51-2.01	
CT scan	**0**	92	41	51	1.00	(Ref.)	0.421 (ns)
	1	78	39	39	0.80	0.44-1.47	
	≥ 2	57	22	35	1.28	0.65-2.51	
Scintigram	**0**	181	80	101	1.00	(Ref.)	0.659 (ns)
	≥ 1	44	22	24	0.86	0.45-1.65	
Mammogram	**0**	190	83	107	1.00	(Ref.)	0.392 (ns)
	≥ 1	37	19	18	0.73	0.36-1.49	
Barium swallow	**0**	209	96	113	1.00	(Ref.)	0.390 (ns)
	≥ 1	18	6	12	1.70	0.61-4.70	
Barium enema	**0**	216	98	118	1.00	(Ref.)	0.560 (ns)
	≥ 1	11	4	7	1.45	0.41-5.11	
Angiogram	**0**	190	85	105	1.00	(Ref.)	0.892 (ns)
	≥ 1	37	17	20	0.95	0.47-1.93	
Intravenous pyelogram	**0**	221	97	124	1.00	(Ref.)	0.093 (ns)
	1	6	5	1	0.16	0.02-1.36	

Table 8. Multivariate analysis: independent risk factors for MDS.

Variable	Category	OR	95% CI	p value
Family history of solid tumor	**No**	1.00	(Ref.)	**0.005**
	Yes	2.47	1.32-4.65	
Consumption of meat	**0-4 days a week**	1.00	(Ref.)	**0.040**
	≥ 5 days a week	2.67	1.05-6.80	
Exposure to pesticides	**No**	1.00	(Ref.)	**<0.0001**
	Yes	3.25	1.73-6.11	

Table 9. Comorbidities in cases and controls (univariate analysis).

Comorbidity	Category	N	Controls	Cases	OR	95% CI	p value
Allergy	**No**	176	67	109	1.00	(Ref.)	**0.001**
	Yes	24	18	6	0.20	0.08-0.54	
Autoimmune disease	**No**	188	82	106	1.00	(Ref.)	0.218 (ns)
	Yes	12	3	9	2.32	0.61-8.85	
Hypertension	**No**	94	30	64	1.00	(Ref.)	**0.005**
	Yes	106	55	51	0.44	0.24-0.77	
Ischemic heart disease	**No**	171	76	95	1.00	(Ref.)	0.181 (ns)
	Yes	29	9	20	1.78	0.77-4.13	
Heart failure	**No**	187	82	105	1.00	(Ref.)	0.156 (ns)
	Yes	13	3	10	2.60	0.69-9.77	
Stroke	**No**	190	82	108	1.00	(Ref.)	0.418 (ns)
	Yes	10	3	7	1.77	0.44-7.06	
Atrial fibrillation	**No**	175	79	96	1.00	(Ref.)	0.052 (ns)
	Yes	25	6	19	2.61	0.99-6.84	
Diabetes mellitus	**No**	154	65	89	1.00	(Ref.)	0.878 (ns)
	Yes	46	20	26	0.95	0.49-1.85	
Thyroid disease	**No**	178	75	103	1.00	(Ref.)	0.766 (ns)
	Yes	22	10	12	0.87	0.36-2.13	
Peptic ulcer	**No**	184	78	106	1.00	(Ref.)	0.916 (ns)
	Yes	16	7	9	0.95	0.34-2.65	
Osteoarthritis	**No**	166	60	106	1.00	(Ref.)	**<0.0001**
	Yes	34	25	9	0.20	0.09-0.46	
Parkinson's disease	**No**	195	82	113	1.00	(Ref.)	0.432 (ns)
	Yes	5	3	2	0.48	0.08-2.96	
Psychiatric disease	**No**	176	74	102	1.00	(Ref.)	0.725 (ns)
	Yes	24	11	13	0.86	0.36-2.02	
Neoplasm	**No**	185	81	104	1.00	(Ref.)	0.155 (ns)
	Yes	16	4	12	2.34	0.73-7.51	
COPD	**No**	182	80	102	1.00	(Ref.)	0.193 (ns)
	Yes	18	5	13	2.04	0.70-5.96	