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Exposure to pesticides and mental disorders in a rural population of Southern Brazil

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ABSTRACT

Introduction: Exposure to pesticides has been associated with mental disorders, especially in occupationally exposed populations, such as farmers. This effect has been attributed to the neurotoxic and endocrine-disrupting activity of pesticides, as suggested by experimental studies.
Objective: To determine the prevalence of common mental disorders and self-reported depression, and analyze their association with the exposure to pesticides in a rural population resident in the municipality of Dom Feliciano, Rio Grande do Sul, where tobacco farming is the main economic activity.
Methodology: A cross-sectional study evaluating the prevalence of common mental disorders and self-reported depression in a sample of 869 adult individuals resident in Dom Feliciano, between October 2011 and March 2012 was performed. The evaluation of common mental disorders was performed using the Self-Reporting Questionnaire (SRQ-20), setting a cutoff point of 8 for both genders. A standardized questionnaire was used to obtain information on self-reported depression upon prior diagnosis by a health professional, and self-reported exposure to pesticide. In order to evaluate the association between exposure to pesticides and mental disorders, a non-conditional multivariate logistic regression analysis was performed.
Results: The prevalence of common mental disorders and self-reported depression in the sample population were 23% and 21%, respectively. Among individuals who reported depression, an increase of 73% was observed in the odds of pesticide exposure at an age equal to or less than 15 years. There was a positive association between self-reported pesticide poisoning and common mental disorders (OR = 2.63; 95% CI, 1.62-4.25) as well as self-reported depression (OR = 2.62; 95% CI, 1.63–4.21). Individuals who reported depression had a greater odds of exposure to pyrethroids (OR = 1.80; 95% CI, 1.01–3.21) and aliphatic alcohol (OR = 1.99; 95% CI, 1.04–3.83). An SRQ–20 $\geq$ 8 was associated with an approximately seven times higher odds of exposure to aliphatic alcohol (95% CI, 1.73–27.53). Self-reported depression positively correlated with a greater period of exposure to dinitroaniline (OR = 2.20; 95% CI, 1.03–4.70) and sulphonylurea (OR = 4.95; 95% CI, 1.06–23.04).
Conclusion: The results suggest that exposure to pesticides could be related mental disorders. However, other common risk factors in tobacco farming, the main local economic activity, cannot be excluded.

1. Introduction

The intensive use of pesticides to prevent, repel or eliminate organisms deemed harmful resulted in the widespread release of these substances into the environment, which is worrisome (Maroni et al., 2000). In the last ten years, the national demand for these substances grew 190% while the world market grew by 93%. In 2008, Brazil became the main market of pesticides in the world, consumption a total of 936 thousand tonnes of these compounds between 2010 and 2011 (ANVISA, 2012).

The intensive use of pesticides is not restricted to large monocultures, they are also common in family farms (Carneiro et al., 2012) that are responsible for a large part of the national internal market supply (Brazil, 2009). However, despite extensive use of pesticides, these workers do not receive adequate technical assistance, which increases their risk of exposure to pesticides (Peres et al., 2001).

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One of the main damages exposure to pesticides causes to human health is endocrine disruption, which is thought to be responsible for the development of cancer, reproductive, immunological and neurodevelopmental problems (WHO, 2002), and neurotoxic effects (Bjørling-Poulsen et al., 2008; Salama et al., 2015). Several studies have suggested that pesticide exposure, such as organochlorine, organophosphate, pyrethroid, is a risk factor for the development of mental disorders, in particular depression (Stallones and Beseler, 2002; Beseler et al., 2006, 2008; Beard et al., 2013; Weisskopf et al., 2013; Faria et al., 2014). However, the results from these studies have been inconsistent, especially concerning the effects of chronic exposure to low doses (Freire and Koifman, 2013), while the association with acute poisoning events has been more apparent (Faria et al., 1999).

In this context, the traditional productive farming of tobacco stands out, with Brazil as the main exporter and the second largest producer in the world (Sinditabaco, 2014). Cultivation of tobacco involves the use of several pesticides, most frequently the organophosphates (OPs) and dithiocarbamates (Etges, 2002). These chemical compounds have been reported to interfere with, for example, the regulation of neurotransmitters such as serotonin, indicating a potential mechanism through which they relate to mental disorders (Aldridge et al., 2005; Slotkin and Seidler, 2008). Dithiocarbamates that have manganese in their composition, such as maneb, could have an effect on dopamine (Bjørling-Poulsen et al., 2008; Burton and Guilarte, 2009). When compared to other population groups, a higher prevalence of mental disorders (Etges, 2002; Poletto and Gontijo, 2012) and mortality by suicide (Silva et al., 2007) have been reported in pesticide applicators.

Mental illness is a public health problem affecting approximately 450 million people worldwide (WHO, 2004). The World Health Organization (WHO) estimates that mental disorders represent 13% of the total number of disability adjusted life years (DALYs) lost (WHO, 2004). The most frequently observed mental disorders are depression and anxiety. Currently, depression affects around 350 million people worldwide (WHO, 2012) and is expected to be the second most important determinant of the global burden of disease by 2020 (Andrews et al., 2000).

A better understanding of the possible risk factors implicated in the development of mental disorders will help in the development of a public health approach to these disorders (Weisskopf et al., 2013). Therefore, the objective of this study was to determine the prevalence of common mental disorders and self-reported depression in relation to pesticide exposure in a rural population resident in the municipality of Dom Feliciano – Rio Grande do Sul (RS), where tobacco farming is the main economic activity.

2. Materials and methods

2.1. Study population

A population survey was conducted between May 2011 and March 2012. Individuals of both genders aged 18 years and older, resident in the municipality of Dom Feliciano – RS, capable of understanding and responding the questionnaires and speaking the Portuguese language were included in the study.

This assessment was conducted from the study entitled "Health and sustainable development in family farming at tobacco producing region", the objective of which was to evaluate the health profile of the population resident in the municipality of Dom Feliciano – RS and the main risk factors for cancer. A population sampling stratified by areas of coverage of the health units was performed, taking microregions and the gender of the individuals into account. The sample estimate was 1024 individuals for the prevalence of nicotine intoxication found in tobacco leaves of 0.184 (Arcury et al., 2008), with an admissible error of 0.025 and a confidence interval of 0.95. A further 23% was added to account for missing data and refusals. The number of residents per area was provided by the staff of Community Health Agent Program and Family Health of Dom Feliciano – RS. During the study, the coverage by the health units was approximately 86% of a population of 14,380 inhabitants (IBGE, 2010), which is equivalent to 12,400 inhabitants and 3991 families. Among these, a total of 8453 (68.2%) residents were within the age range determined for inclusion. Of the 1024 eligible, 155 (15.1%) individuals were assumed to be lost to the study, 23 could not be located, and 132 refused to participate. The final sample was comprised of 869 participants (84.9%). According to the sample calculation of the study conducted by Faria et al. (2014) with an assumed true prevalence of 0.20 for common mental disorders, the sample size of the present study is equivalent to the estimated sample size (n = 882 individuals).

This study was approved by the Ethics Committee of the National Cancer Institute José Alencar Gomes da Silva – INCA (N° 120/09) and all individuals who agreed to participate in the study signed a Free and Informed Consent Form.

2.2. Questionnaire

The interviews were performed by health agents and trained local supervisors of the Municipal Health Secretariat staff, using a questionnaire structured in the form of anamnesis. The interviews were conducted in private room, in the participant's home, after telephone contact to mark the time. The participants were surveyed in two stages: 1) The period of tobacco cultivation, aiming to distinguish frameworks of pesticide poisoning and 2) The period of tobacco harvest, suggestive of greater exposure to nicotine due to increased contact with the leaves. The first stage was conducted between August and October 2011 and the second between January and February 2012.

We used a general questionnaire to collect individual data on identification, domicile, risk perception, general conditions of health, women's health, food insecurity, work, agriculture, use of transgenic seeds, tobacco farming and use of pesticides and a clinical questionnaire to collect information on acute intoxication and exposure to pesticides by chemical group. While both questionnaires were conducted in the first stage, only the clinical questionnaire was conducted in the second stage. However, in this study, we used the dates of first stage, because the tobacco cultivation period has most pesticide exposure, and less nicotine contact. In order to determine the condition of food insecurity, the Brazilian Food Insecurity Scale was included in the general questionnaire. This scale is composed of 15 questions, each with an assigned score of 1 for each affirmative response, and a zero score for food security, further categorized by a scale of 1–5 for light food insecurity, 6–10 for mild food insecurity, and 11–15 as severe food insecurity (Segall-Cerrêa et al., 2003). In this study, food insecurity was treated as a dichotomous variable with food security having an assigned score of zero, and food insecurity an assigned score greater than or equal to one. Under general health conditions, alcoholism emerged from the four questions that constitute the CAGE questionnaire, which were also included in the general assessment. In accordance with the CAGE, a score equal to or greater than two indicates alcohol abuse or dependence (Bernadt et al., 1982).

In this study the following variables were investigated: common mental disorders (yes/no); self-reported depression (yes/no); gender (male/female); age (years; $\leq$25, 26–35, 36–45, 46–55, 56–65, >65 years); skin color (non-white/white); schooling (years; middle school or more/up to elementary education); currently works (yes/no); food insecurity (yes/no); self-reported osteoarticular disease (yes/no) based on a previous clinical diagnosis of spinal or back problems, tendinitis or repetitive strain injury (RSI) and arthritis or rheumatism; alcoholism (yes/no); age at drinking onset (years; >15/≤15 years); smoking (never smoked/ex-smoker/passive smoker/active smoker); age at smoking onset (years; >15/≤15 years); agricultural occupation (yes, currently/yes, in the past/no); works (worked) in tobacco farming (yes/no); cotinine level (mg/g creatinine); self-reported exposure to pesticides (yes/no); duration of pesticide exposure (years; geometric mean); age at onset of pesticide exposure (years; >15/≤15 years); self-reported illness after use of pesticides (yes/no); and use of personal protection equipment (PPE), such as the joint use of gloves, mask, boots and overalls or sleeved shirt and long trousers (yes/no).

2.3. Laboratory analysis

Urine samples were collected in both stages of research for cotinine analysis. In this study were used coninine levels of tobacco cultivation stage.

The urine samples were separated, identified, frozen and properly transported and sent to the laboratory. Cotinine levels were analyzed for enzyme immunoassay (EIA). All supplies for EIA were purchase from OraSure Technologies, Inc., using a kit (662498/2012-05). Cotinine level was adjusted by urine creatinine, that was measured by final point colorimetric (Jaffe modified method) (Junge et al., 2004).

The toxicological analysis was performed at the Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro State, on 2012 period.

2.4. Mental disorders

Metal disorders support a wide variety of problems, with different signs and symptoms. Thus, we point out that, in this study, the term mental disorders refer only to common mental disorders and depression.

2.4.1. Common mental disorders

The evaluation of common mental disorders was performed using the Self-Reporting Questionnaire (SRQ-20), validity to the Brazilian population (Gonçalves et al., 2008). The SRQ-20 is recommended by the WHO for screening of common mental disorders in community studies and basic care in developing countries, due to its practicality and low cost (Gonçalves et al., 2008). This scale was incorporated into the general questionnaire along with the other issues of the module of general health conditions, conducted by the professionals of the team of the Municipal Health Secretariat. In the SRQ-20 application, the participants were instructed to report the last three months to capture some effects of the sales period of the harvest of the previous cycle (between June and July month).

The SRQ-20 is composed of 20 questions directed to identify psychosomatic symptoms associated with non-psychotic disorders (Supplementary material). This is a reduced version of the original composed of 30 questions, which also includes the screening of psychotic disorders and alcohol use disorders (WHO, 1994). In this study, we used a cutoff point of 8, where a score equal to or greater than 8 is considered as positive for common mental disorders. According to the validation of the SRQ-20 performed with a population sample from Santa Cruz do Sul – RS, this cutoff point corresponds to the highest sensitivity (86.3%) and specificity (89.3%) achieved for both genders (Gonçalves et al., 2008). However, for purposes of comparison with other studies, cutoff points equal to 7 for both genders were also analyzed alongside the cutoff of 6 for men and 8 for women (Mari and Williams, 1986; Harpham et al., 2003).

2.4.2. Self-reported depression

The self-reported depression outcome (yes/no) from a previous clinical diagnosis was obtained through a question incorporated into the general health conditions module of the general assessment questionnaire, to which the participant responded whether any doctor or health professional diagnosed him/her with depression.

Given the nature of self-reported data collected in this study, the use of the term "depression" does not differentiate this diagnosis as a symptom, syndrome or disease (Porto and Alberto, 1999).

2.5. Statistical analyses

A descriptive analysis of the characteristics of the study population was performed by means of frequency distribution and univariate analysis of categorical variables using the chi-square test. The mean value and respective standard deviations were calculated for the continuous variables. The geometric mean of the duration of pesticide exposure was calculated in order to smooth out the distribution.

The normality of the continuous variables was evaluated using the Kolmogorov-Smirnov test. Bivariate analyses were conducted using the nonparametric Spearman's rank correlation coefficient, Mann-Whitney *U* test and chi-square group comparisons.

The variables "exposure to pesticides" and "being ill after pesticide exposure" were treated as categorical variables (yes/no). The onset age for pesticide exposure was treated as continuous and categorical (years; >15/≤15 years). The duration of exposure to different chemical groups of pesticides was treated as categorical (≤ or > geometric mean in years). Common mental disorder (cutoff point = 8) outcome, and self-reported depression (yes/no) were treated as categorical variables.

To determine the association between exposure to pesticides and the occurrence of common mental disorders and self-reported depression, non-conditional logistic multivariate regression was performed. The models included the variables associated with the exposure to pesticides and the outcomes of interest in the bivariate analyses, with statistical significance level of $p \leq 0.20$. The variables with $p \leq 0.05$ or those which modified the beta coefficient of the regression of exposure variable on the outcome by 10% or more were maintained in the models. Finally, as recommended in the literature, all models were adjusted by gender, age and socioeconomic level indicators including food security and/or level of schooling, independent of statistical significance. To reduce the multiple comparisons problems of chemical groups analysis, it was applied the Bonferroni correction ($p \leq 0.004$).

The statistical analyses of the data collected were performed using the Statistical Package for Social Sciences (SPSS) for Windows – version 17.0.

3. Results

3.1. Population characteristics

Table 1 shows the characteristics of the study population. The total sample was composed of 869 individuals, equally distributed between sexes, and with age range of 18–89 years. The data collected on the socioeconomic characteristics showed that 83% of participants studied only until elementary education, 22% lived with food insecurity and 81% worked at the time of the evaluation. Osteoarticular disease was reported by 43% of the individuals. Data

Table 1
Characteristics of the study population, Dom Feliciano – RS, 2011–2012.

	n	%	mean (SD)	p-Value[*]
Demographic variables				
Gender	869			
Male	431	49.6		0.81
Female	438	50.4		
Age in evaluation (years)	863		43.4 (16.4)	
≤25	137	15.9		**≤0.01**
26 |–| 35	181	21.0		
36 |–| 45	191	22.1		
46 |–| 55	155	18.0		
56 |–| 65	97	11.2		
>65	102	11.8		
Skin color	865			
Not White	161	18.6		**≤0.01**
White	704	81.4		
Socioeconomic variables				
Schooling (years)	805		5,7 (3,4)	
High School or higher schooling	137	17.0		**≤0.01**
Up to elementary education	668	83.0		
Currently works	868			
Yes	704	81.1		**≤0.01**
Not	164	18.9		
Food security	840			
Yes	658	78.3		**≤0.01**
Not	182	21.7		
Health Variables				
Osteoarticular Disease[a]	843			
No	483	57.3		**≤0.01**
Yes	360	42.7		
Smoking	869			
Never smoked	324	37.3		**≤0.01**
Ex-smokers	128	14.7		
Passive Smoker	162	18.6		
Active smoker	255	29.3		
Age at the onset of smoking (years)	371		16.6 (5.7)	
>15	195	52.6		0.32
≤15	176	47.4		
Excessive use of alcohol (CAGE)	365			
No	295	80.8		**≤0.01**
Yes	70	19.2		
Age at the onset of alcohol consumption (years)	610		17.0 (4.6)	
>15	361	59.2		**≤0.01**
≤15	249	40.8		
Variables of agricultural practices				
Works in agriculture	869			
Not	97	11.2		**≤0.01**
Yes, currently	548	63.1		
Yes, in the past	224	25.8		
Works(ed) with tobacco farming	868			
No	154	17.7		**≤0.01**
Yes	714	82.3		
Cotinine level (ng/mL)	808		400.3 (695.8)	
Cotinine level (mg/g)	807		1.2 (11.8)	
Exposure to Pesticides	866			
No	243	28.1		**≤0.01**
Yes	623	71.9		
Age at the onset of pesticide exposure (years)	590		21.0 (9.7)	
>15	395	66.9		**≤0.01**
≤15	195	33.1		
Felt ill after use of pesticides	400			
No	289	72.3		**≤0.01**
Yes	111	27.8		
Use of full PPE[b]				
Yes	78	13.5		**≤0.01**
No	499	86.5		

Bold values refer to test results with statistical significance level ≤0.05.
[*] Chi-square test.
[a] Spine or back disease, tendinitis or repetitive strain injury, arthritis or rheumatism.
[b] Full PPE (personal protection equipment) = joint use of gloves, mask, overalls or sleeved shirt and pants, and boots.

collected on the environmental exposures showed that 29% of the population was active smokers. From the 365 respondents of the CAGE questionnaire, 19% were classified as having abusive or dependent alcohol consumption. The mean onset age of smoking and alcohol consumption was 17 years and 47% of the smokers and 41% of the alcohol consumers acquired these habits before the age of 15 years. From the total number of participants, 89% were working/worked at some point of time in agriculture, and 82% were working/worked in tobacco farming.

Three participants out of the 869 had lost information of exposure to pesticides. The prevalence of exposure to these substances in the population was 72%. Participants were exposed to pesticides in different activities, 58% exposed to apply, 53% prepare the mixture of compounds, 48% help in the application (e.g. handling the pesticide pump), 53% transporting or handle compounds, 39% enter the crop immediately after application of pesticides, 53% help in cleaning the equipment and 45% help in washing the clothes used in the application of pesticides. All activities were most developed by man, except cleaning the clothes, which was done principally by women (Data not shown in the table).

Among the 623 individuals exposed to pesticides, 590 provided information on the age of onset of exposure, of which 33% were equal to or less than 15 years. Only 400 individuals informed about having been ill after applying pesticides, with 28% responding affirmatively. The information on PPE use was supplied by 577 participants, only 14% of which jointly used mask, gloves, boots and overalls or pants and long-sleeved shirt (Table 1).

Table 2 describes the pesticides used by the agricultural population, by chemical group. Active ingredients belonging to 31 distinct chemical groups were identified. Considering only the pesticides the chemical groups of which were surveyed in the questionnaire (excluding the category "other"), the most used were isoxazolidinone (80%), dinitroaniline (77%), dicarboximide (68%), substituted glycine (65%) and pyrethroids (61%). The frequency of less than 5% use of the benzoylurea, bipyridylium and pyrazol pesticides prevented association studies through multivariate analysis among these substances and the outcomes analyzed.

Table 2
Pesticides used by the agricultural population, Dom Feliciano – RS, 2011–2012.

Chemical group	N (total)	Users N (%)
Ariloxialcanoic acid	486	64 (13.2)
Ariloxiphenoxi-propionic acid	489	175 (35.8)
Aliphatic alcohol	488	272 (55.7)
Benzoylurea	486	10 (2.7)
Bipyridylium	484	13 (2.7)
Dicarboximide	490	334 (68.2)
Dinitroaniline	490	379 (77.3)
Substituted Glycine	489	318 (65.0)
Aliphatic Hydrocarbon	487	177 (36.3)
Inorganic	487	283 (58.1)
Isoxazolidinone	491	393 (80.0)
Organochlorine	488	78 (16.0)
Organophosphate	488	262 (53.7)
Pyrazol	485	24 (4.9)
Pyrethroid	490	298 (60.8)
Sulphonylurea	489	86 (17.6)
Other[a]	492	458 (93.1)

Trade names inquired: ariloxialcanoic acid = aminol, tordon, 2,4-D, DMA 806; ariloxiphenoxi-propionic acid = fusilade; aliphatic alcohol = antak; benzoylurea = nomolt; bipyridylium = gramoxone; dicarboximide = rovral; dinitroaniline = herbadox, primeplus; substituted glycine = round up, glyphosate; aliphatic hydrocarbon = assist; inorganic = copper sandox, gastoxin; isoxazolidinones = gamit; organochlorine = thiodan; organophosphate = acephate fersol, cefanol, lebaycid, lorsban; pyrazol = klap; pyrethroid = decis, karate, talstar; sulphonylurea = sanson, nicosulfuron.

[a] Other = halogenated aliphatic; carbamate and benzamide pyridine; dithiocarbamate; dithiocarbamate and acilalaninate; dithiocarbamate and carbamate; dithiocarbamate and benzimidazole; dithiocarbamate and cetamide; dithiocarbamate and inorganic; benzofuranyl methylcarbamate; naphthyl methylcarbamate; neonicotinoid; neonicotinoid and pyrethroid; organophosphate and aromatic hydrocarbon; organophosphate, pyrethroid and hydrocarbon; cyclohexanedione oxime; pyrazol and fluoroaliphatic sulfonamide; fluoroaliphatic sulfonamide; triazine; triazolone.

3.2. Common mental disorders

Among the 869 participants, 840 answered the SRQ-20 fully. A prevalence of 23% was observed for common mental disorders (Table 3). Using a cutoff point of 7 for both genders, a prevalence of 29% was observed. The separate analysis by gender, using the cutoff points of 6 for men and 8 for women, indicated a prevalence of 22% and 33%, respectively.

Multivariate analysis showed almost three-fold odds of feeling ill after the use of pesticides among the individuals with SRQ–20 $\geq$ 8 points (95% CI, 1.62–4.25) when compared to those with a score <8 (Table 4). The same result was observed for the cutoff point of 7 for both genders (OR = 2.32; 95% CI, 1.44–3.73), 6 for men, and 8 for women (OR = 1.85; 95% CI, 1.16–2.94) (Data not shown in the table).

The results of the multivariate analysis for the use of pesticides by chemical group are summarized in Table 5. An almost seven fold higher odds of exposure to aliphatic alcohol for individuals with SRQ–20 $\geq$ 8 points was observed (95% CI, 1.73–27.53). A greater odds of exposure to pyrethroids was also observed for individuals with common mental disorders, with a borderline statistical significance (OR = 2.21; 95% CI, 0.99–4.96). Although the results suggest a greater odds of exposure for individuals with score $\geq$8 to aryloxyalcanoic acid, aliphatic hydrocarbons and isoxazolidinone, the odds ratios were not statistically significant (Table 5).

A positive correlation between the duration of exposure to 11 of 13 chemical groups analyzed and SRQ–20 $\geq$ 8 points was observed in the models when considering the duration of exposure to pesticides, but without statistical significance (Table 6).

Applying the Bonferroni correction on chemical groups analysis, no association was significant (p-value $\leq$ 0.004).

3.3. Self-reported depression

The question regarding a previous diagnosis of depression was answered by 844 participants, with a prevalence of 21% (Table 3).

The logistic regression analysis showed a 2.6 times higher odds of feeling ill after use of pesticides among the participants who reported a previous diagnosis of depression when compared to

Table 3
Prevalence of mental disorders in the study population, Dom Feliciano – RS, 2011–2012.

Mental disorders	n	%	p-value*
Common mental disorders			
Self-Reporting Questionnaire (SRQ-20)	840		
Both genders			
Score < 8	646	76.9	**≤0.01**
Score ≥ 8	194	23.1	
Score < 7	601	71.5	**≤0.01**
Score ≥ 7	239	28.5	
Score < 6 men; < 8 women	612	72.9	**≤0.01**
Score ≥ 6 men; ≥ 8 women	228	27.1	
Men	424		
Score < 6	331	78.1	**≤0.01**
Score ≥ 6	93	21.9	
Women	416		
Score < 8	281	67.5	**≤0.01**
Score ≥ 8	135	32.5	
Self-reported depression	844		
No	665	78.8	**≤0.01**
Yes	179	21.2	

Bold values refer to test results with statistical significance level ≤0.05.
* Chi-square test.

Table 4
Multivariate logistic regression between mental disorders and exposure to pesticides.

	Common mental disorders (SRQ-20)			Self-reported depression		
	OR	95% CI	p-value	OR	95%CI	p-value
Exposure to pesticides (ref = no)[a,e]	1.06	0.68–1.67	0.789	1.07	0.70–1.62	0.764
Felt ill after application of pesticides (ref = no)[b;f]	**2.63**	**1.62–4.25**	**<0.001**	**2.62**	**1.63–4.21**	**0.001**
Use of pesticides from age ≤15 years (ref = >15 years)[c,g]	1.43	0.87–2.36	0,160	**1.73**	**1.07–2.80**	**0.026**
Age when started the use of pesticides (years)[d,h]	1.00	0.97–1.03	0.793	0.99	0.96–1.01	0.305

Bold values refer to test results with statistical significance level ≤0.05.
Score of common mental disorders obtained by the SRQ–20 = Self-Reporting Questionnaire; cutoff point SRQ-20 = 8 for both genders. OR = odds ratios. CI = confidence interval. Ref = reference category. SRQ-20, each OR corresponds to a model adjusted for the variables: [a]gender, categorized age, categorized schooling, food security, smoking; [b]gender, categorized age, food security, osteoarticular disease; [c]gender, continuous age, years of study, smoking; [d]gender, categorized age, years of study, food security, osteoarticular disease, smoking. Depression, where each OR corresponds to a model adjusted for the variables: [e]gender, age categorized, food security, smoking; [f]gender, categorized age, osteoarticular disease, food security; [g]gender, continuous age, smoking, food security; [h]gender, categorized age, food security, osteoarticular disease, smoking.

Table 5
Multivariate logistic regression between mental disorders and exposure to pesticides by chemical group.

Use of from pesticides (ref = no)	Common mental disorders (SRQ-20)			Self-reported depression		
	OR	95%CI	p-value	OR	95%CI	p-value
Ariloxialcanoic acid[a,m]	2.62	0.78–8.84	0,120	1.96	0.91–4.22	0,086
Ariloxiphenoxi-propionic acid[b,n]	0.85	0.47–1.55	0,603	0.95	0.53–1.73	0,869
Aliphatic alcohol[c,o]	**6.90**	**1.73–27.53**	**0,006**	**1.99**	**1.04–3.83**	**0,039**
Dicarboximide[d,n]	1.03	0.58–1.80	0,930	1.44	0.79–2.63	0,230
Dinitroaniline[e,m]	0.76	0.43–1.33	0,337	1.04	0.57–1.88	0,897
Substituted glycine[f,p]	0.78	0.26–2.33	0,649	1,10	0.61–1.99	0,761
Aliphatic hydrocarbon[d,n]	1.56	0.89–2.74	0,122	1.67	0.95–2.93	0,075
Inorganic[g,q]	0.97	0.57–1.65	0,906	1.19	0.66–2.15	0,560
Isoxazolidinone[h,r]	7.82	0.37–164.22	0,186	1.51	0.76–2.99	0,243
Organochlorine[i,s]	0.40	0.08–2.13	0,284	1.64	0.82–3.25	0,160
Organophosphate[j,t]	0.76	0.45–1.29	0,302	1.05	0.62–1.78	0,865
Pyrethroid[k,u]	2.21	0.99–4.96	0,054	**1.80**	**1.01–3.21**	**0,047**
Sulfonylurea[l,m]	0.85	0.39–1.86	0,689	1.17	0.59–2.35	0,651

Bold values refer to test results with statistical significance level ≤0.05.
Score of common mental disorders obtained by the SRQ–20 = Self-Reporting Questionnaire; cutoff point SRQ-20 = 8 for both genders. OR = odds ratios. CI = confidence interval. Ref = reference category.
SRQ-20, each OR corresponds to a model adjusted for the variables: [a]gender, categorized age, years of study, CAGE; [b]gender, categorized age, years of study, smoking; [c]gender, categorized age, food security, CAGE; [d]gender, categorized age, food security, smoking; [e]gender, continuous age, food security; [f]gender, continuous age, years of study, food security, CAGE; [g]gender, continuous age, food security, osteoarticular disease; [h]gender, categorized age, food security, age began smoking (continuous), CAGE; [i]gender, categorized age, years of study, smoking, CAGE; [j]gender, continuous age, years of study, osteoarticular disease; [k]gender, continuous age, years of study, age began smoking (categorical); [l]gender, categorized age, years of study, food security. Depression, each OR corresponds to a model adjusted for the variables: [m]gender, continuous age, food security; [n]gender, continuous age, smoking, food security; [o]gender, categorical age, years of study, smoking, food security, osteoarticular disease; [p]gender, continuous age, categorized schooling, smoking, food security; [q]gender, categorized age, categorized schooling, food security, osteoarticular disease; [r]gender, categorized age, food security, osteoarticular disease; [s]gender, categorized age, smoking, osteoarticular disease, food security; [t]gender, continuous age, osteoarticular disease, food security; [u]gender, continuous age, smoking, osteoarticular disease, food safety.

those without the diagnosis (Table 4). A statistically significant positive association was observed between onset age of pesticide exposure in ages up to 15 years and self-reported depression (OR = 1.73; 95% CI, 1.07–2.80).

The analysis of the association between exposure to specific types of pesticides and self-reported depression showed a greater odds of exposure to aliphatic alcohol (OR = 1.99; 95% CI, 1.04–3.83) and pyrethroids (OR = 1.80; 95% CI, 1.01–3.21) (Table 5). Although statistically insignificant, all other results suggest a greater odds of exposure to pesticides analyzed among the individuals who reported depression, with the exception of arylphenoxy-propionic acid (Table 5).

Individuals who reported depression presented a five times greater odds of having been exposed to sulfonylurea for a period exceeding four years (95% CI, 1.06–23.04). A positive association was also observed between a larger period of exposure to dinitroaniline and self-reported depression (OR = 2.20; 95% CI, 1.03–4.70) (Table 6). For the other pesticides analyzed, no statistically significant association was observed between duration of use and self-reported depression. Applying the Bonferroni correction, no association was significant (p-value ≤ 0.004).

4. Discussion

In the present study, a prevalence of common mental disorders and self-reported depression observed were 23% and 21%, respectively. Feeling ill after the use of pesticides was positively associated with the presence of common mental disorders and self-reported depression. An increase of 73% in the odds of exposure to pesticides was observed at an onset age of 15 years or younger among the individuals who reported depression. The use of pesticides in the aliphatic alcohol chemical group was positively associated with common mental disorders and self-reported depression and the use of pyrethroids was positively associated with self-reported depression. A greater period of use of dinitroaniline and sulfonylurea chemical groups was associated with self-reported depression. However, no association was significant in chemical groups models using a more stringent criteria in the analysis.

Several studies have reported a different prevalence of common mental disorders (Faria et al., 1999, 2014; Poletto and Gontijo, 2012), which diverges more or less when compared with the values observed for the population of Dom Feliciano. A study performed

Table 6
Multivariate logistic regression between mental disorders and time of exposure to pesticides by chemical group.

Time of use of pesticides (years)	Common mental disorders (SRQ-20)			Self-reported depression		
	OR	95%CI	p-value	OR	95%CI	p-value
Ariloxialcanoic acid[a,i]						
Up to 3 years	1	Reference		1	Reference	
4 years or more	0.57	0.13–2.55	0,462	2.71	0.58–12,79	0,207
Ariloxiphenoxi-propionic acid[b,j]						
Up to 5 years	1	Reference		1	Reference	
6 years or more	1.53	0.55–4.24	0,413	1.48	0.53–4.12	0,452
Aliphatic alcohol [a,k]						
Up to 9 years	1	Reference		1	Reference	
10 years or more	1.08	0.56–2.08	0,811	1.34	0.66–2.72	0,419
Dicarboximide[c,k]						
Up to 8 years	1	Reference		1	Reference	
9 years or more	1.03	0.49–2.17	0,933	1.24	0.60–2.55	0,534
Dinitroaniline[d,k]						
Up to 9 years	1	Reference		1	Reference	
10 years or more	0.54	0.17–1.78	0,311	**2.20**	**1.03–4.70**	**0,042**
Substituted glycine[e,j]						
Up to 5 years	1	Reference		1	Reference	
6 years or more	1.73	0.84–3.55	0,137	1.44	0.74–2.83	0,285
Aliphatic hydrocarbon[e,l]						
Up to 3 years	1	Reference		1	Reference	
4 years or more	2,18	0.85–5.58	0,104	1.14	0.49–2.68	0,762
Inorganic[f,l]						
Up to 8 years	1	Reference		1	Reference	
9 years or more	1.35	0.58–3.16	0,487	0.79	0.38–1.62	0,788
Isoxazolidinone[e,k]						
Up to 8 years	1	Reference		1	Reference	
9 years or more	1.40	0.73–2.68	0,308	1.36	0.72–2.59	0,346
Organochlorine[a,j]						
Up to 7 years	1	Reference		1	Reference	
8 years or more	3.03	0.84–10.94	0,091	1.99	0.60–6.58	0,258
Organophosphate[a,m]						
Up to 9 years	1	Reference		1	Reference	
10 years or more	1.71	0.77–3.78	0,187	1.13	0.53–2.44	0,751
Pyrethroid[g,n]						
Up to 5 years	1	Reference		1	Reference	
6 years or more	1.70	0.34–8.48	0,519	0.79	0.38–1.64	0,520
Sulfonylurea[h,j]						
Up to 4 years	1	Reference		1	Reference	
5 years or more	1.46	0.23–9.32	0,687	**4.95**	**1.06–23.04**	**0,041**

Bold values refer to test results with statistical significance level $\leq$0.05.
Score of common mental disorders obtained by the SRQ–20 = Self-Reporting Questionnaire; cutoff point SRQ-20 = 8 for both genders. OR = odds ratios. CI = confidence interval. SRQ-20, each OR corresponds to a model adjusted for the variables: [a]gender, continuous age, food security; [b]gender, continuous age, years of study, food security; [c]gender, categorized age, smoking, food security, osteoarticular disease; [d]gender, categorized age, CAGE, food security; [e]gender, categorized age, food security; [f]gender, categorized age, years of study, food security; [g]gender, continuous age, CAGE, food security, age when started smoking (continuous); [h]gender, continuous age, food security, age when started smoking (categorized). Depression, each OR corresponds to a model adjusted for the variables: [i]gender, continuous age, years of study; [j]gender, continuous age, food security; [k]gender, categorized age, food security, osteoarticular disease; [l]gender, categorized age, food security; [m]gender, continuous age, food security, osteoarticular disease; [n]gender, continuous age, categorized schooling, food security, osteoarticular disease.

on farmers who grow tobacco in São Lourenço do Sul – RS, reported a 9.2% prevalence of common mental disorders (Faria et al., 2014), using the same cutoff point as this study. However, when assessing the agricultural population of Antonio Prado and Ipê – RS, the same research team observed a 38% prevalence in the score of the SRQ–20 $\geq$ 6 for men and $\geq$8 for women (Faria et al., 1999), while in Dom Feliciano, for this cutoff point, a prevalence of 27% was observed. The variability of the prevalence of common mental disorders could be attributed to high sensitivity of the SRQ-20, being able to positively identify a large spectrum of affections that result in mental suffering, and the possibility of variation of symptoms depending on the personal and professional life of the individuals (Porto et al., 2006).

The prevalence of self-reported depression indicated in this study (21%) was higher than the one often reported in previous studies (Stallones and Beseler, 2002; Beseler et al., 2006, 2008; Beseler and Stallones, 2008; Beard et al., 2013, 2014; Onwuameze et al., 2013; Weisskopf et al., 2013). In the USA, a study using Center for Epidemiologic Studies-Depression (CES-D) Scale showed a 6% prevalence of depression for agricultural workers and their spouses (Stallones and Beseler, 2002). Three other studies in the USA reported a prevalence of self-reported depression from a previous clinical diagnosis equal to 8% for farmers (Beard et al., 2014) and 6–7% for spouses of farmers (Beseler et al., 2006; Beard et al., 2013). Likewise, French farmers showed a 15% prevalence of self-reported of had been traded or hospitalized for depression (Weisskopf et al., 2013). The greater prevalence of depression reports observed in the population of Dom Feliciano could be explained by the predominance of tobacco farming as the main source of income in the region (82%). Although the studies conducted in the USA and France investigated agricultural populations, it is known that tobacco production is particularly exhaustive, demanding an extensive workload and multiple exposures, not only to pesticides, but also to nicotine (Faria et al., 2014), in addition to the common indebtedness and economic dependence of the producers to the industry (Reis et al., 2015), which combined may have contributed to the greater prevalence of self-reported depression.

The analysis of the use of pesticides, without differentiation by chemical groups showed no significant association with the evaluated outcomes. However, corroborating the results of previous studies, a positive association was observed between feeling ill after the use of pesticides, indicating an acute intoxication by these substances, and common mental disorders (Faria et al., 1999, 2014; Poletto and Gontijo, 2012) and self-reported depression (Beseler et al., 2006; Beseler and Stallones, 2008; Beard et al., 2014).

The exposure to pesticides at the age of 15 or younger was positively associated with self-reported depression. This result can be explained by the greater vulnerability of children and adolescents to neurotoxic substance exposure, since the development of the central nervous system begins in the gestational period and extends until adolescence (Rice and Barone, 2000; Ernst and Korelitz, 2009).

The results of the analysis performed by chemical group are difficult to compare with the literature. Most of the studies in this area did not analyze the pesticides by chemical group or restrict the assessment to the effect of organochlorine (OC), OP and carbamate exposure, and the information is limited for the other groups used (Faria et al., 1999, 2014; Stallones and Beseler, 2002; Beseler et al., 2006, 2008; Beseler and Stallones, 2008; Poletto and Gontijo, 2012; Beard et al., 2013, 2014; Onwuameze et al., 2013; Weisskopf et al., 2013). To our knowledge, no other study has investigated the effects of exposure to aliphatic alcohol on the development of mental disorders, in which a statistically significant positive association was observed. However, as in this study, where part of the significant associations occurred with herbicides (dinitroaniline and sulphonylurea), a study conducted with French farmers reported a greater odds of exposure to this type of pesticides (Weisskopf et al., 2013). However, individual analysis of the pesticides showed no significant association between depression and dinitroaniline (Weisskopf et al., 2013). A study performed in Brazilian tobacco growers showed an inverse association between exposure to dinitroaniline and common mental disorders (Faria et al., 2014).

In a study conducted in the USA regarding pyrethroids; insecticides widely used in agriculture, a positive association was observed between exposure to pesticides of this functional group and depression in applicators (Beseler et al., 2008). Furthermore, corroborating the findings of this study, a North American study that evaluated a cohort of farmer spouses reported a positive association between exposure to pyrethroids and depression (Beard et al., 2013).

The effects of exposure to aliphatic alcohol have been poorly explored, both in experimental and epidemiological studies (EPA, 2007), which limits the understanding of the potential mechanisms by which these substances result in the investigated outcomes. Concerning sulphonylureas, an experimental study conducted in fish displayed a neurotoxic effect due to the inhibition of acetylcholinesterase activity (Bretaud et al., 2000). Although, in principle, cholinergic alterations are not related to development mechanism of mental disorders, it is possible that similar to other cholinesterase inhibitors, such as organophosphates (Bjørling-Poulsen et al., 2008), sulphonylureas also adversely affect monoaminergic neurotransmitters, which could explain the possible depressive effect of exposure to these substances.

Some studies have suggested an antidepressant effect of pyrethroids by activation of the gene expression of brain-derived neurotrophic factor (Tsai, 2006; Takasaki et al., 2013). However, these compounds are able to bind to thyroid receptors and exert antithyroid activity (Du et al., 2010), affecting the homeostasis of these hormones (Meeker et al., 2009). Likewise, experimental evidence suggests that dinitroaniline pesticides can induce the activity of the enzyme uridine diphosphate glucuronyl transferase, increasing the excretion of thyroid hormones (Hurley, 1998). Given that both hypothyroidism and hyperthyroidism have been associated with depression (Ittermann et al., 2015), the results found for these pesticides may be considered biologically plausible.

In the present study, no association was observed between the outcomes analyzed and exposure to ariloxialcanoic acid, ariloxiphenoxi-propionic acid, dicarboximide, substituted glycine, aliphatic hydrocarbon, inorganic, isoxazolidinone, OP and OC.

The ability of the OC pesticides to deregulate monoaminergic neurotransmitters (Lakshmana and Raju, 1994; Schuh et al., 2009), and the homeostasis of thyroid hormones (Boas et al., 2012), may enable these substances to cause psychological alterations. However, the low use of these substances in Dom Feliciano (16%) may have made the observation of a statistically significant association in this study impossible. The low frequency of OC usage may be explained by the prohibition of the use and marketing of pesticides of this chemical group in Brazil in the 1980s (Ministério da Agricultura, 1985), restricting the use of compounds such as endosulfan, also known as thiodan – withdrawn from the market in July 2013 (ANVISA, 2010), on specific crops and in combating disease vectors in public health campaigns (Ministério da Agricultura, 1985).

Although the OP are widely used in the cultivation of tobacco, and are considered a possible risk factor for mental disorders due to their ability to target neurotransmitters (Aldridge et al., 2005; Slotkin and Seidler, 2008), in contrast to majority of the studies (Beseler et al., 2008; Beard et al., 2014; Faria et al., 2014), no association was observed between exposure to these pesticides and the outcomes analyzed in the population of Dom Feliciano. If the occurrence of outcomes depend on the intensive exposure to these substances, a possible absence of symptoms of acute intoxication by this and other chemical groups could be responsible for the failure to form associations (Weisskopf et al., 2013). Another factor that must be considered is the possibility of classification bias in the study. In this respect, it is worth highlighting that mainly among women, reporting of agricultural work and not the exposure to pesticides was observed, while tobacco farming is strongly linked to their usage (Faria et al., 2014). Studies of risk perception concerning this matter have demonstrated that generally, women farmers do not see themselves as users of pesticides, since even when participating in the preparation or implementation of these substances they consider these activities as secondary (Peres et al., 2004, 2006). Given that the greater prevalence of common mental disorders and self-reported depression was observed in women (women and men, respectively: $SRQ \geq 8 = 32.5\%$ *versus* 13.9%; depression = 28.7% *versus* 13.2%), the possible error of exposure rating between them may have hindered the observation of statistically significant associations, for both the OP and for other pesticides.

Farmers use simultaneously many compounds with different actions mode. Thus, analyze using overall pesticides use may be the results diluted effects, while analyze of chemical groups of pesticide can be confounded the results (Campos and Freire, in press). In addition, a limitation of the study was the possibility of having incurred in memory bias by the loss of quality of information obtained by recall. Another limitation is the absence of information on marital status; an important covariable in the study of mental disorders, as well as exposure to pesticides of the dithiocarbamate and carbamate groups, since they are used in large quantities in tobacco farming (Etges, 2002) and/or because of present neurotoxic effects (Aldridge et al., 2005; Bjørling-Poulsen et al., 2008; Slotkin and Seidler, 2008; Burton and Guilarte, 2009).

Regarding exposure measurement, although the internal dose is the most indicated form of determination to pesticide exposure, many non-persistent pesticides do not have biomarkers available, or reflect recent exposure. Thus, the use of questionnaire information is an alternative to overcome these limitations (Campos and Freire, in press).

The temporal limitation of cross-sectional design does not permit this study deducing causal relationship, but suggest association between pesticide exposure and mental disorders. Concerning the methods implemented, it is necessary to emphasize that the WHO recommends the application of SRQ-20 for the last 30 days (WHO, 1994). However, in the present study, while applying the SRQ-20, the participants were instructed that they should report the last three months, which may have compromised the validity of the test. In addition, it is important to highlight the limitation that the SRQ-20 score is only suggestive and not diagnostic (Porto et al., 2006), ideally used as screening tool. Moreover, given the sensitivity of the SRQ-20 to identify a wide range of affections that trigger positive mental suffering, as well as the characteristic seasonality of symptoms already observed in some categories of workers (Porto et al., 2006), the implementation of this instrument reduces the ability of this study in making inferences about mental disorders *per se*. However, this is an easily applicable and frequently implemented instrument, which enables the comparison of our results with other studies. With regard to self-reported diagnosis of depression, this also presents low validity. However, we believe that any possibility of classification bias is reduced by the fact that the opinion of a health professional was involved in the self-reported depression. Finally, among the strengths of this study, we can highlight the size of the sample and the quantity of chemical groups analyzed, for some of which only scarce information can be found in the literature.

5. Conclusion

The results suggest that poisoning by pesticides can be associated to mental disorders, and shows increased odds by exposure to dinitroaniline, pyrethroids, sulfonylurea and aliphatic alcohol. In addition, the study suggests an association between a self-reported early exposure to pesticides and mental disorders. However, one cannot exclude other risk factors common to individuals who work with tobacco farming, predominant in the region studied, such as exhausting work, indebtedness and economic dependence.

The intensive use of pesticides in agriculture, in particular tobacco plantations, and the growing onset of mental disorders, renders this issue of extreme importance for public health. Moreover, we highlight the necessity of further studies in this area, preferably with longitudinal design and drawing implementing more specific diagnostic tools in order to more accurately analyses the relationship between exposure to different types of pesticides and the development of mental disorders.

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Conflict of interest

No potential conflict of interest.

Author contributions

Élida Campos – statistical analysis, data interpretation and elaboration of manuscript;

Valéria dos Santos P. da Silva – critical review;

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neuro.2016.06.002.

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