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## NeuroToxicology



# Occupational exposure to pesticides, nicotine and minor psychiatric disorders among tobacco farmers in southern Brazil

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### ABSTRACT

**Introduction:** Exposure to pesticides has been associated with psychiatric problems among farm workers, although there is still controversy as to chemical types, intensity and forms of exposure that represent risk factors for neuropsychological problems. Furthermore, tobacco workers are exposed to dermal absorption of nicotine, although its effect on mental health has not yet been studied.

**Objectives:** To identify the prevalence of minor psychiatric disorders (MPD) among tobacco farmers and associated factors, paying special attention to pesticide and nicotine exposure.

**Methods:** This is a cross-sectional study with a representative sample of tobacco growers, characterizing economic indicators of the farms, socio-demographic factors, lifestyle habits and occupational exposures. Multivariate analysis was performed using a hierarchical Poisson regression model.

**Results:** A total of 2400 tobacco farmers were assessed and MPD prevalence was 12%. MPD was higher among women (PR 1.4), workers aged 40 or over, tenants/employees (PR 1.8) and those who reported having difficulty in paying debts (PR 2.0). Low socioeconomic status was inversely associated with MPD prevalence. Tasks involving dermal exposure to pesticides showed risk varying between 35% and 71%, whereas tobacco growers on farms using organophosphates had 50% more risk of MPD than those not exposed to this kind of pesticide. The number of pesticide poisoning and green tobacco sickness episodes showed linear association with MPD.

**Conclusions:** The study reinforces the evidence of the association between pesticide poisoning and mental health disorders. It also points to increased risk of MPD from low socioeconomic status, dermal pesticide exposure as well as from exposure to organophosphates. Furthermore, the study reveals intense nicotine exposure as a risk for tobacco farmers' mental health.

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## 1. Introduction

Intensive pesticide use has been accompanied by increased concern about the potential acute and chronic effects of pesticides on health in general and on mental health in particular. In Brazil, a country with a large number of farm workers, this problem is of great relevance. Brazil has been the world's largest pesticide consumer since 2008. Consumption has increased 190% in the last decade, considerably above average global growth of 93% (ANVISA, 2012).

Several studies have found association between pesticide poisoning and psychiatric problems, especially depression (London

et al., 2005, 2012; Stallones and Beseler, 2002; Faria et al., 1999; Wesseling et al., 2010; Beseler et al., 2006, 2008; Beseler and Stallones, 2008) among farmers and farm workers. Moreover studies in Brazil (Meyer et al., 2010; Poletto and Gontijo, 2012), Spain (Parron et al., 2011) and the USA (Beseler et al., 2008; Mackenzie Ross et al., 2010) have identified association between pesticide exposure and psychiatric problems. A study conducted with fruit farmers in the Brazilian state of Rio Grande do Sul found association between pesticide poisoning and increased prevalence of minor psychiatric disorders (MPD) (Faria et al., 1999). Another Brazilian study, conducted in the state of Rio de Janeiro, documented higher rates of hospitalizations owing to mood disorders and suicide attempts among those living in areas with more intensive pesticide use (Meyer et al., 2010). However, controversy remains as to the effect of routine pesticide use – not involving acute poisoning – and the occurrence of psychiatric problems among agricultural workers (London et al., 2005, 2012; Wesseling et al., 2010; Keifer and Firestone, 2007).

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In addition to intense exposure to pesticides, frequently multichemical, other forms of occupational exposure in agriculture may also be mental health risk factors, such as strenuous work, long working days and farming production losses. Studies among farmers in Brazil (Meyer et al., 2010; Poletto and Gontijo, 2012) and in several other parts of the world (London et al., 2012; Wesseling et al., 2010; Kim et al., 2013; Hounsborne et al., 2012; Sanne et al., 2004) relate agricultural activity to excessive stress and/or mental suffering (Roy et al., 2013).

Tobacco production is seasonal and involves annual production cycles. This crop is characterized by intensive pesticide use and a large number of workers directly exposed to these chemicals. In Brazil more than 220,000 families are involved in tobacco production. The country is the world's second largest tobacco producer and has been the world's leading exporter since 1993 (Sindiabaco, 2013). Some studies indicate increased prevalence of psychiatric problems among tobacco growers in southern Brazil (Poletto and Gontijo, 2012). However, the prevalence of mental health problems and associated risks factors in this group of workers are not clear. In addition to pesticides and other chemical risks common to other farming activities, these workers are also heavily exposed to dermal absorption of nicotine (Fassa et al., 2014). However, the effect of these exposures on worker's mental health is not clear.

This study aims to identify MPD prevalence among tobacco growers and associated factors, paying special attention to pesticide and nicotine exposure.

## 2. Methods

A cross-sectional study was conducted with tobacco farmers in São Lourenço do Sul-RS in southern Brazil. According to the 2010 Census, this town had around 43,100 inhabitants, 44% of whom were living in the rural area. Most of the population is German descent (Pomeranian ethnicity and Lutheran religion). Its economy is based on tourism and agriculture, mainly tobacco (it is the second largest producer in Southern Brazil) and grains (rice, soybeans and corn) (IBGE, 2014).

The sample size was estimated so as to measure 20% MPD prevalence with a 2.0 pp margin of error and associations with a prevalence ratio greater than 1.8, a 95% confidence level, 80% statistical power and a 14:1 unexposed: exposed ratio with regard to pesticide poisoning. A further 10% was added to account for missing data and refusals as well as 15% for confounding factors. The sample size required was about 2600 workers. Based on an estimated of 2.5 workers per farm, 1040 farms needed to be studied.

The sample was selected based on invoices issued in 2009 for tobacco sales, which is mandatory for all sales of agricultural products. A total of 1100 invoices (database obtained in the Municipal Agriculture Office) were selected randomly and the farms (agricultural establishment or production unit) that issued the invoices were identified.

The Brazilian Agricultural-Census-IBGE (2006) (Censo Agropecuario, 2013) considered a production unit to be any productive structure under the same management. Following to this criterion, all agricultural establishments, dedicated to tobacco production activities (fully or partially) under the same management were included regardless of size. At each farm, all workers aged 18 or over engaged in farming activities for at least 15 h a week were selected (Faria et al., 1999). The workers were interviewed at their farms and the fieldwork covered a period of around eight weeks, during the 2011 harvest (January and February).

The majority of the interviewers had been community health workers and/or Brazilian Census interviewers, who lived in the region being studied. They received training to perform the interviews and to use Personal Digital Assistants for data input.

Two questionnaires were used. The first questionnaire characterized the farms and obtained economic indicators such as their area, amount of tobacco produced annually, other agricultural production, degree of mechanization, ownership of vehicles, financial debts and crop diversification (based on the proportion of income arising from tobacco production). The types of pesticides used were informed by the farm operator by looking at cards containing photographs and the trade names of the 56 pesticides most used in the region.

The second questionnaire assessed each worker and examined socio-demographic factors (gender, age, marital status and schooling), history of suicide in the family, employment status (owner or tenant/employee), lifestyle habits (smoking and alcohol consumption, religion practiced), occupational exposures, comorbidities and mental health. Smoking was categorized as non-smoker, smoker (one cigarette or more per day) former smoker (stopped smoking a month or more ago) and alcohol consumption according to the number of daily units drunk on weekdays. Types of occupational exposure to pesticides were assessed, such as applying, mixing, loading the sprayer tank, cleaning equipment, entering a treated area following application, washing contaminated clothing, being exposed during transportation and storage, having contact through soaked clothes with pesticide during application and having contact with leaves containing pesticide residues. Intensity of exposure was evaluated by the sum of these nine types of exposure, and categorizing this information in four groups (none; up to four types; five to six; seven to nine types). Monthly exposure frequency and type of personal protective equipment (PPE) used were also investigated. Cumulative exposure was estimated based on years of exposure to pesticides.

Assessment of comorbidities included the number of pesticide poisoning episodes during workers' lives based on information reported by them. Chronic low back pain (CLBP) was considered to be indicated by complaints of pain lasting for three months a year or more. Green tobacco sickness (GTS) was characterized by the number of episodes of headache or dizziness together with nausea or vomiting in the previous year occurring after contact with tobacco leaves (Arcury et al., 2008, 2003). The outcome – minor psychiatric disorders (MPD) – defined as non psychotic mental disorders, was assessed using the SRQ-20 questionnaire. The Self-Reporting Questionnaire 20 items (SRQ-20) is derived from four psychiatric morbidity instruments with a wide variety of cultural backgrounds. It was developed by Harding et al. (1980) for a WHO collaborative study to screen for common mental disorders in primary health care (Harding et al., 1980; Harpham et al., 2003).

SRQ-20 reflects the multidimensional nature of 'mental illness' screening for disorders such as depression, anxiety and somatic disorders. Factor analyses have shown that one group of SRQ-20 questions taps into a somatic factors (headaches, appetite, digestion, sleep); another into depressive/anxiety symptoms (frightened, unhappy, crying, feeling worthless); while a third captures more cognitive/decreased energy factors (not able to concentrate or make decisions, suffering at work, unable to enjoy daily activities) (Harpham et al., 2003). The SRQ-20 is a cost-effective way to measure mental health and was considered to be positive if there were six or more answers showing alteration in men and eight or more answers showing alteration in women (Mari and Williams, 1986). For the purpose of comparison with other studies, SRQ-20 prevalence was also described considering other cut-off points: tests with seven and eight answers showing alteration in both genders were considered as positive results (Harpham et al., 2003; Mari and Williams, 1986).

For descriptive analysis, continuous variables (such as age, schooling, tobacco production, percentage of income from tobacco, days per month of exposure, years of exposure and others) were categorized. Variables representing intensity of exposure and

cumulative exposure were examined as quartiles or terciles. The description of the variables assessed prevalence using Pearson's chi-square test, as well as, mean and standard deviation. Multivariate analysis was performed by Poisson regression with robust variance estimation (using *Stata 11*), providing Prevalence Ratio as a measure of effect. Crude and Adjusted analyses used Wald heterogeneity test and Wald linear trend test. These analyses followed a hierarchical model with backward selection whereby variables with  $p \leq 0.2$  were maintained in the model. Associations having  $p < 0.05$  were considered to be significant. The hierarchical levels were organized as follows:

**Level 1:** Demographic factors (gender, age), employment status, economic indicators (annual tobacco production, difficulty in paying debts, vehicle ownership, percentage of income arising from tobacco) and family history of suicide.

**Level 2:** Lifestyle habits (smoking and alcohol consumption), religious activity, occupational exposures (working hours spent on agricultural activities, intense working pace, tasks requiring strenuous work); and pesticide exposure (types of individual exposure, intensity of exposure, frequency of use).

**Level 3:** Comorbidities: green tobacco sickness (GTS), chronic low back pain (CLBP) and pesticide poisoning.

Cumulative exposure was found to have significant correlation with age (Pearson correlation = 0.46). Therefore, in order to examine the association between years of chemical exposure and MPD, the same hierarchical model was used, excluding age from level 1 and including cumulative exposure in level 2.

The association between the ten most used chemical types and MPD was assessed. Pesticides associated with the outcome with  $p \leq 0.2$  (organophosphates – OP, glyphosate, triazine and flumetralin) were examined using multivariate analysis following the same hierarchical model, excluding forms of individual exposure and including types of chemicals in level 2. Interactions between GTS and pesticide poisoning, as well as, between OP and GTS were checked.

This study was submitted to and approved by the Federal University of Pelotas Research Ethics Committee. All participants voluntarily signed the consent form. Cases identified as having health problems were referred for free of charge treatment.

### 3. Results

A total of 2400 tobacco growers answered the SRQ-20 questionnaire and were included in this analysis. Losses and refusals totalled 7.7% of eligible workers.

### 4. Characteristics of the farms and the workers studied

The farms had an average planted area of 7.7 hectares of tobacco (sd = 12.4), with average production of 5.6 tonnes per annum (sd = 4.4) and maximum production of 36 tonnes per annum. The majority of farms had five or more agricultural machines/implements. Around half the farms stated that they produced other crops such as corn, beans and potatoes; as well as products of animal origin such as milk (26.1%) and honey (17.5%).

Half the tobacco growers worked on farms where more than 80% of income arose from tobacco production and which had at least one vehicle (automobile/lorry/pick-up truck). On average there were three workers per farm, 95% of whom were members of the family owning the farm whilst the remainder were tenants or employees. In terms of economic problems faced by the farms, 21.5% reported difficulties in paying financial debts (Table 1).

The majority of the tobacco growers were men (59.3%) (Table 1) and over 90% of them were descendants of Pomeranian Germans. Average age was 39.5 (sd = 13.0) – varying between 18 and 79 years of age – average duration of schooling was 5.2 complete

**Table 1**

Association between demographic and socioeconomic factors and minor psychiatric disorders (MPD), 2011 ( $n = 2400$ ).

Socio-economic and demographic variables	N	%	MPD %	P
Total sample	2400	100%	12.0	
Annual tobacco production				<0.001 <sup>b</sup>
Up to 2500 kg	156	6.5	21.8	
2501–5000 kg	667	27.9	14.5	
5001–10,000 kg	1051	43.9	11.4	
10,001–36,000 kg	518	21.7	6.9	
% Income from tobacco				0.16 <sup>b</sup>
Up to 70%	680	28.4	10.7	
71–80%	547	22.8	11.7	
81–95%	588	24.6	12.6	
96% or more	579	24.2	13.1	
Owns a car or truck/vehicles				<0.001 <sup>b</sup>
No	368	15.4	19.3	
One	1394	58.3	11.6	
Two or more	631	26.4	8.6	
Employment Status				0.004 <sup>a</sup>
Farm owners (farmers)	2282	95.1	11.6	
Tenants/employees	118	4.9	20.3	
Difficulty in paying debts				<0.001 <sup>a</sup>
No	1872	78.2	9.3	
Yes	522	21.8	21.5	
Gender				0.004 <sup>a</sup>
Male	1422	59.3	10.4	
Female	977	40.7	14.3	
Age				0.01 <sup>a</sup>
18–29 years	676	28.2	9.0	
30–39 years	555	23.1	11.7	
40–49 years	548	22.8	15.3	
≥50 years	621	25.9	12.6	
Schooling				0.7 <sup>a</sup>
Up to 3 years	286	11.9	13.3	
4–7 years	1692	70.5	11.8	
8 years or more	422	17.6	12.1	
Suicide in the family				0.03 <sup>a</sup>
No	2096	87.3	11.5	
Yes	304	12.7	15.8	
Lifestyle habits				
Smoking				0.24 <sup>a</sup>
Never smoked	1614	67.2	11.9	
Former smoker	315	13.1	14.6	
Smoker	471	19.6	10.6	
Alcohol consumption: number of units drunk on weekdays				0.02 <sup>a</sup>
None	1665	69.6	13.2	
Occasional	472	19.7	8.5	
Up to one unit	154	6.4	8.4	
2 units or more	103	4.3	13.6	
Participation in religious activities				0.001 <sup>a</sup>
No	77	3.2	23.4	
Sometimes	1581	65.9	10.6	
Frequently	741	30.9	13.8	

<sup>a</sup> Chi-square test.

<sup>b</sup> Linear trend test.

years (sd = 2.7) and 12.7% had a history of suicide in the family (Table 1).

Around 20% were smokers and 13% stated they were former smokers. 4.3% consumed two or more daily units of alcoholic beverage on weekdays, whilst 69.6% did not drink on weekdays. The vast majority took part in religious activities (the majority were Lutheran) and 31% did so frequently (Table 1).

During the harvest they worked 11.6 h a day on average undertaking agricultural activities (sd = 2.7) and 13.5 h a day (sd = 2.7) when taking all kinds of work into account. The pace of work was considered to be intense during more than three months a year by the majority of the tobacco growers (58%) and 64% stated that their agricultural activities required strenuous work (Table 1).

66% reported direct contact with pesticides in their agricultural work during the last twelve months. Over half the tobacco growers

reported applying pesticides, mixing and loading the sprayer tank during the last year. Half the workers had cleaned pesticide equipment. More than 30% had washed clothes contaminated during pesticide application and had had contact with leaves containing pesticide residues or with clothes wet from pesticide. Around 20% had entered the treated area following pesticide application or had had contact during transportation. At least 17% of the tobacco growers used pesticides ten or more days a month (Table 2).

Pesticides were used on practically all farms (99.4%). The most used chemical groups were: flumetralin (91.8%), clomazone (86.8%), neonicotinoids (77.7%), dithiocarbamate (69.0%), glyphosate (65.4%), organophosphate (63.2%), metalaxyl (55.9%), sulfentrazone (42.8%) iprodione (36.4%), pyrethroids (34.0%) and triazine (23.2%).

Most tobacco growers (60%) had more than ten years of cumulative exposure to pesticides and 17% had worked with pesticides for more than thirty years. With regard to comorbidities, 8% had CLBP, 4.7% reported four or more episodes of GTS in the previous year and 7% reported at least one episode of pesticide poisoning in their lives (Table 2).

## 5. Minor psychiatric morbidity

MPD prevalence was 12%, when SRQ test results with 6 answers showing alterations for men and 8 for women were considered to be positive (10.4% for men and 14.3% for women) (Table 1). This criterion was used in the multivariate analysis. This prevalence was similar to prevalence obtained when SRQ test with 7 altered answers for both genders were used, with some differences according to gender (7.7% for men and 18.6% for women). When was used the cut-off point of 8 altered answers for both genders, the prevalence was 9.2% (5.7% for men and 14.3% for women).

In the multivariate analysis, MPD prevalence was higher among women (prevalence ratio-(PR) 1.4), people aged 40 and over, tenants/employees (PR 1.8) and also among those who reported having difficulty in paying debts (PR 2.0). Tobacco production volume was inversely associated with MPD prevalence. Moderate participation in religious activities and occasional consumption of alcohol on weekdays demonstrated a protective effect in relation to MPD (Table 3).

With regard to the effect of occupational exposures, longer working hours spent on agricultural activities were found to be inversely associated with MPD prevalence, whilst strenuous work showed increased risk of MPD (PR 1.8). The pesticide intensity

Table 2 (Continued)

Occupational exposure	N	%	MPD%	P
1–8 days	1148	48.0	12.5	
9 days or more	417	17.4	12.2	
Applying pesticides				0.68 <sup>a</sup>
No	897	37.4	12.4	
Yes	1500	62.6	11.8	
Mixing pesticides				0.41 <sup>a</sup>
No	1045	43.6	12.6	
Yes	1352	56.4	11.5	
Loading tank				0.30 <sup>a</sup>
No	1023	42.7	12.8	
Yes	1374	57.3	11.4	
Cleaning equipment				0.82 <sup>a</sup>
No	1089	45.4	11.8	
Yes	1308	54.6	12.2	
Washing clothes contaminated during application				<0.002 <sup>a</sup>
No	1534	64.0	10.5	
Yes	864	36.0	14.7	
Entering the treated area following application				<0.001 <sup>a</sup>
No	1908	79.6	9.9	
Yes	490	20.4	20.2	
Has contact with leaves containing pesticide residues				<0.006 <sup>a</sup>
No	1588	66.2	9.9	
Yes	809	33.8	16.1	
Has contact through clothes wet from pesticides				<0.001 <sup>a</sup>
No	1647	68.7	9.9	
Yes	751	31.3	16.6	
Has contact during transportation				0.001 <sup>a</sup>
No	1802	75.2	10.7	
Yes	594	24.8	16.0	
Intensive exposure (related to nine above types of pesticide exposure)				0.001 <sup>b</sup>
None	676	28.2	11.2	
One to four ways of exposure	570	23.8	9.5	
Five to six ways of exposure	633	26.5	10.0	
Seven to nine ways of exposure	514	21.5	18.5	
Cumulative exposure to pesticides				0.009 <sup>b</sup>
No exposure	464	19.5	11.0	
Up to 9 years	507	21.3	8.1	
10–19 years	524	22.0	13.0	
20–29 years	488	20.5	13.9	
30 years or more	399	16.8	14.3	
Pesticide use on the farm				
Uses Organophosphates				0.001 <sup>a</sup>
No	880	36.8	9.1	
Yes	1514	63.2	13.7	
Uses glyphosate				0.002 <sup>a</sup>
No	829	34.6	14.8	
Yes	1565	65.4	10.5	
Uses triazine				0.08 <sup>a</sup>
No	1838	76.8	12.6	
Yes	556	23.2	9.9	
Uses Flumetralin				<0.001 <sup>a</sup>
No	196	8.2	20.4	
Yes	2198	91.8	11.2	
Comorbidities				
Chronic low back pain (≥3 months)				<0.001 <sup>a</sup>
No	2196	91.5	10.0	
Yes	203	8.5	33.5	
Green Tobacco Sickness (number of episodes in the last year)				<0.001 <sup>b</sup>
None	2111	88.7	9.0	
1–3 episodes	155	6.5	25.8	
≥4 episodes	113	4.7	46.9	
Pesticide poisoning (number of episodes during lifetime)				<0.001 <sup>b</sup>
None	2219	92.9	10.5	
1 episode	119	5.0	23.5	
≥2 episodes	50	2.1	44.0	

<sup>a</sup> Chi-square test.

<sup>b</sup> Linear trend test.

Table 2

Association between occupational exposure, pesticide poisoning, comorbidities and minor psychiatric disorders, 2011 (*n* = 2400).

Occupational exposure	N	%	MPD%	P
Farm working day during harvest				0.02 <sup>a</sup>
Up to 8 h/day	307	12.8	16.6	
9–12 h/day	1327	55.5	10.9	
13–18 h/day	759	31.7	11.9	
Intense working pace				0.001 <sup>b</sup>
Up to 3 months	1012	42.3	10.2	
4–7 months	1117	46.7	11.7	
8 months or more	262	11.0	19.1	
Heavy strength at work				<0.001 <sup>a</sup>
No	858	35.8	8.7	
Yes	1542	64.2	13.8	
Individual types of pesticide exposure				0.13 <sup>a</sup>
Contact with pesticides (last year)				
No	811	33.8	10.6	
Yes	1588	66.2	12.7	
Frequency of use: days per month				0.56 <sup>a</sup>
Does not use pesticides	826	34.5	10.9	



**Table 3**Multivariate analysis: factors associated with minor psychiatric disorders ( $n = 2400$ ).

1st Level – variables	Unadjusted PR (CI 95%)	Adjusted PR(CI 95%)	P value adjusted
Annual tobacco production (kg)			<0.001 <sup>b</sup>
Up to 2500	3.14 (2.03–4.84)	2.34 (1.51–3.63)	
2501–5000	2.09 (1.45–3.01)	1.72 (1.19–2.49)	
5001–10,000	1.64 (1.15–2.35)	1.54 (1.08–2.19)	
10,001–36,000	1	1	
Employment status			0.002 <sup>a</sup>
Farm owners	1	1	
Tenants/employees	1.76 (1.21–2.56)	1.82 (1.25–2.65)	
Difficulty in paying debts			<0.001 <sup>a</sup>
No	1	1	
Yes	2.30 (1.85–2.85)	2.02 (1.61–2.53)	
Gender			0.003 <sup>a</sup>
Male	1	1	
Female	1.38 (1.11–1.71)	1.39 (1.12–1.72)	
Age			0.01 <sup>b</sup>
18–29	1	1	
30–39	1.30 (0.93–1.81)	1.33 (0.96–1.85)	
40–49	1.70 (1.25–2.32)	1.61 (1.18–2.19)	
≥50	1.39 (1.01–1.91)	1.42 (1.03–1.95)	
2nd Level – variables			
Alcohol consumption: number of units drunk on weekdays			0.1 <sup>b</sup>
None	1	1	
Occasional	0.64(0.47–0.88)	0.68(0.49–0.95)	
Up to one unit	0.64(0.37–1.09)	0.64(0.37–1.08)	
Two units or more	1.03(0.62–1.70)	0.93(0.57–1.51)	
Participation in religious activities			0.003 <sup>a</sup>
No	1	1	
Sometimes	0.45 (0.30–0.70)	0.50 (0.32–0.78)	
Frequently	0.59 (0.38–0.92)	0.65 (0.41–1.02)	
Occupation exposure			
Farm work during harvest			0.002 <sup>a</sup>
Farm working day			
Up to 8 h/day	1	1	
9–12 h/day	0.66 (0.49–0.88)	0.59 (0.44–0.79)	
13–18 h/day	0.71 (0.52–0.98)	0.62 (0.44–0.87)	
Having strenuous work			<0.001 <sup>a</sup>
No	1	1	
Yes	1.58 (1.23–2.03)	1.73 (1.32–2.26)	
Exposure to pesticides			
Intense exposure (related to nine types of pesticide exposure)			<0.001 <sup>b</sup>
None	1	1	
One to four types of exposure	0.84 (0.61–1.17)	0.99 (0.71–1.39)	
Five to six types of exposure	0.89 (0.65–1.21)	1.03 (0.74–1.45)	
Seven to nine types of exposure	1.64 (1.24–2.17)	1.88 (1.38–2.57)	
3rd Level – comorbidities			
Number of pesticide poisonings episodes (lifetime)			<0.001 <sup>b</sup>
None	1	1	
1 episode	2.24 (1.59–3.17)	1.55 (1.10–2.18)	
2 or more episodes	4.19 (3.00–5.86)	2.45 (1.75–3.43)	
Number of green tobacco sickness episodes (last year)			<0.001 <sup>b</sup>
None	1	1	
Up to 3	2.85(2.11–3.85)	2.14(1.57–2.90)	
≥4	5.18(4.08–6.58)	3.07(2.37–3.97)	
Chronic low back pain			<0.001 <sup>a</sup>
No	1	1	
Yes	3.43 (2.65–4.21)	2.24 (1.76–2.85)	

<sup>a</sup> Wald heterogeneity test.<sup>b</sup> Wald trend test.

exposure indicator showed linear association with MPD, with 88% of increased risk for those having seven or more types of pesticide exposure. In relation to comorbidities, the number of pesticide poisoning and green tobacco sickness episodes showed direct linear association with MPD, whilst CLBP increased the risk of MPD by 100% (Table 3).

Among the different forms of exposure to pesticide, entering the treated area following pesticide application and having contact with soaked clothes with pesticides showed respectively 71% and 35% increased risk of MPD (Table 4).

The multivariate analysis for cumulative exposure presented direct association with MPD, with linear trend (Table 4).

When examining the association between types of chemicals and MPD, after adjustment for confounding factors, tobacco growers working on farms using organophosphates showed 50% more risk of MPD than those working on farms where this type of pesticide was not used. A prevalence ratio of 0.67 was found among those working on farms using flumetralin (Table 5).

No interactions between OP and GTS related to MPD risk were found. On the other hand, GTS and pesticide poisoning presented a significant interaction ( $p = 0.03$ ). Multivariable analyses examining workers without GTS showed stronger association between pesticide poisoning and MPD. On the other hand, the association between GTS and MPD was stronger in those who did not have

**Table 4**Multivariate analysis: types of pesticide exposure, cumulative exposure (years of exposure to pesticides) and MPD ( $n=2400$ ).

Types of pesticide exposure <sup>c</sup>	Unadjusted PR (CI 95%)	Adjusted PR (CI 95%)	Adjusted <i>P</i> value
Washing clothes contaminated during application			0.9 <sup>a</sup>
No	1	1	
Yes	1.40(1.13–1.74)	0.93(0.78–1.26)	
Entering the treated area following application			<0.001 <sup>a</sup>
No	1	1	
Yes	2.04(1.63–2.55)	1.71(1.33–2.20)	
Has contact with leaves containing pesticide residues			0.07 <sup>a</sup>
No	1	1	
Yes	1.61(1.30–2.00)	1.27(0.99–1.64)	
Has contact through clothes wet from pesticides			<0.004 <sup>a</sup>
No	1	1	
Yes	1.68 (1.35–2.09)	1.35 (1.06–1.73)	
Has contact during transportation			0.6 <sup>a</sup>
No	1	1	
Yes	1.49 (1.19–1.87)	1.06 (0.81–1.39)	
Cumulative pesticide exposure <sup>d</sup>			0.01 <sup>b</sup>
Years of exposure			
Unexposed	1	1	
Up to 9 years	0.76 (0.52–1.12)	0.70 (0.45–1.06)	
10–19 years	1.26 (0.90–1.77)	1.11 (0.75–1.65)	
20–29 years	1.35 (0.97–1.89)	1.22 (0.83–1.81)	
30 years or more	1.39 (0.98–1.97)	1.25 (0.85–1.83)	

All variables were adjusted for: gender, tobacco production, employment status, debts, alcohol consumption, religious activity, farming workday and strenuous work.

<sup>a</sup> Wald heterogeneity test.<sup>b</sup> Wald trend test.<sup>c</sup> Regression model includes age, but does not include intense exposure.<sup>d</sup> Regression model includes intense exposure, but does not include age.**Table 5**Multivariate analysis: types of chemicals used on the farm in the last year and MPD ( $n=2400$ ).

Pesticide use	Unadjusted PR (CI 95%)	Adjusted PR (CI 95%)	<i>p</i>
Uses organophosphates			0.001 <sup>a</sup>
No	1	1	
Yes	1.50 (1.18–1.92)	1.52 (1.19–1.94)	
Uses glyphosate			0.06 <sup>a</sup>
No	1	1	
Yes	0.71 (0.57–0.88)	0.81 (0.65–1.01)	
Uses triazine			0.8 <sup>a</sup>
No	1	1	
Yes	0.78 (0.59–1.04)	1.03 (0.78–1.36)	
Uses flumetralin			<0.01 <sup>a</sup>
No	1	1	
Yes	0.55 (0.41–0.74)	0.67 (0.49–0.91)	

All variables were adjusted for gender, age, tobacco production, employment status, debts, alcohol consumption, religious activity, farming workday and strenuous work.

Regression model does not include types of individual pesticide exposure.

<sup>a</sup> Wald heterogeneity test.

pesticide poisoning. Therefore when pesticide poisoning and GTS are included in the same model, the risk of MPD is underestimated, although the effect remains still strong. Moreover, the associated variables in all those models remain the same.

## 6. Discussion

This study showed that the number of lifetime pesticide poisoning episodes and the number of green tobacco sickness episodes in the last year (nicotine poisoning) are directly associated with MPD in family tobacco farm workers. Types of individual pesticide exposure involving dermal contact as well as the use of organophosphates on the farms are associated with higher risk for MPD. The study involved a large and representative sample of tobacco farm workers. There were few losses and this reinforces the study's internal validity.

Studies with fruit farmers (MPD = 36%) (Faria et al., 1999) and tobacco growers (33%) (Poletto and Gontijo, 2012), conducted in southern Brazil, evaluating MPD using SRQ-20, found higher prevalence than this study (12%). Other studies using SRQ-20 with an urban population in the same region found prevalence of 22.7% and 28.5% (Costa et al., 2002), whilst prevalence was 16% among health professionals (Dilelio et al., 2012). Locating the farms selected and obtaining consent to conduct the study were facilitated owing to the interviewers living locally. However, the fact that the interviewers were often known by the respondents may have generated biased information underestimating MPD prevalence (Faria et al., 1999). A third of the losses were related to the SRQ-20 not being fully answered, which reinforces this idea. On the other hand, income from tobacco production appears to be higher than that from other crops produced on family farms (Agostinotto et al., 2000) and this may contribute to lower MPD prevalence among tobacco growers.

Tobacco growers working on farms producing less tobacco, those with difficulties in paying debts and employees/tenants had higher MPD prevalence when compared to farm owners. This finding is consistent with studies showing inverse association between a variety of economic indicators and mental disorders (Beseler and Stallones, 2008; Beseler et al., 2008; Pulkki-Raback et al., 2012). As in the case of other crops, tobacco producers are also subject to losses resulting from unfavourable climatic conditions. Moreover, they face pressure when negotiating the sale of their tobacco and this may be even more difficult for small producers.

Consistent with other publications regarding rural studies (Faria et al., 1999; Gregoire, 2002) or studies with the general population (Costa et al., 2002), women have higher MPD prevalence than men, even when analysing SRQ-20 using a higher cut-off point for women. In their validation study Mari and Williams (1986) recommended a lower score for men (due to a higher false negative rate in men) considering gender differences in illness behaviour. Higher prevalence among women might be related to cultural aspects which allow women to express their suffering more easily. Gender has been considered a critical

determinant of mental health, showing higher prevalence of anxiety, depression and somatic disorders among women (WHO, 2004) – these being the main disorders measured by SRQ-20. These findings are in agreement with this study. Moreover, the additional female overburden from housework also could contribute to this result.

MPD was more frequent among the older age group – mainly those aged 40 or over (starting from 30 and with a slight reduction after 50). This result is in agreement with other studies with farm workers (Faria et al., 1999; Poletto and Gontijo, 2012; Kim et al., 2013) and with the study involving the urban population (Costa et al., 2002), but is quite different from studies with other groups of workers such as health professionals, with lower risk among those 50 or more (Dilelio et al., 2012). In some studies, age was not associated with psychiatric disorders (Stallones and Beseler, 2002; Meyer et al., 2010). In others it increased up until a certain age and reduced among the elderly (Beseler et al., 2008).

Occasional consumption of alcoholic beverages on weekdays was associated with lower risk of MPD. This result indicates that individuals with poorer health or who take medication for mental health problems may avoid consuming alcohol. This is consistent with the Agricultural Health Study, which found lower prevalence of psychiatric problems in groups with moderate alcohol consumption (Beseler et al., 2008). Moderate practicing of religious activities had a protective effect in relation to MPD. This result agrees with a Brazilian study which found a higher frequency of psychiatric problems (particularly bipolar disorders), related to the intensity of religious practices, whereby such problems were worse among the non-religious or among the very religious (Soeiro et al., 2008).

Longer working hours spent on agricultural activities during harvesting were inversely associated with MPD. This may be related to the healthy worker effect (Agerbo, 2005) but may also include a residual effect of income, given that the longest working hours occurred among farmers involved with larger tobacco production volumes. On the other hand, those who reported performing strenuous work had higher MPD prevalence. This result may reflect heat-related illness that is common in hot environments and in physical exertion, such as agricultural activities, mainly in the harvest and during the summer (NIOSH, 2013). Agriculture is one of the industries at highest risk of heat-related illness. Otherwise, “adverse long term effects of workplace heat exposure have been reported such as mental health problems” (Xiang et al., 2013). Thus, in addition to having symptoms which overlap with other comorbidities, heat exposure could be one of the determinants of mental health disorders.

Tobacco growers having seven or more types of pesticide exposure, i.e. involving intense contact with chemical products, have increased MPD prevalence. Moreover, types of exposure involving greater dermal contact (entering the treated area following pesticide application and wearing soaked clothes with pesticides), were found to be associated with increased MPD. The main route of occupational absorption of pesticides is through the skin (Macfarlane et al., 2013), including chemical products known to be neurotoxic such as organophosphates, which have already been associated with psychiatric problems in several agricultural contexts (London et al., 2005; Wesseling et al., 2010; Beseler et al., 2008; Keifer and Firestone, 2007). As the interviews took place in the summer, excessive heat may also have increased the absorption of both pesticides and nicotine, owing to peripheral vasodilatation (Macfarlane et al., 2013).

Cumulative exposure, i.e. the number of years of exposure to pesticides, was directly associated with MPD. This result suggests a chronic effect of pesticide exposure on mental health. Cumulative pesticide exposure was identified as a risk factor for depression by the Agricultural Health Study. However, the criteria used to define cumulative exposure were different, thus limiting comparisons (Beseler et al., 2008).

In this study organophosphates were the only chemical group positively associated with MPD (Table 5). The main toxic mechanism of these chemicals is cholinesterase inhibition, leading to acute intoxication and cholinergic syndrome in particular. Studies among farm workers have revealed association between intensive organophosphate use and mental health problems such as depression (London et al., 2005, 2012; Wesseling et al., 2010). Studies with animals have indicated alterations of the serotonergic system as a result of chronic exposure to the pesticide methamidophos-(organophosphate) at levels below the threshold for cholinergic hyperstimulation. Behavioural effects were similar to those of depression (Lima et al., 2009, 2011). In contrast to this result, the use of the anti-sprouting agent flumetralin was found to be inversely associated with MPD (Table 5). This product is used principally in the topping stage and those who did not use it had poorer economic indicators. This may indicate a residual effect of income. Moreover, no evidence of flumetralin neurotoxicity was found (Reregistration Eligibility Decision, 2007). The specification of the pesticides used on the farms was qualified by using cards with photographs and names of the main products used in the region. This strategy improved the workers' recall and helped the correct identification of product names.

CLBP was positively associated with MPD. The presence of chronic diseases, in particular diseases producing pain, is a factor known to cause mental suffering among workers (Andrade et al., 2013). On the other hand, recognition must be given to the possible bi-directionality of the association between CLBP and mental health problems which are frequently reproduced in a vicious circle (Andrade et al., 2013).

The number of green tobacco sickness episodes in the previous year and the number of lifetime pesticide poisoning episodes were directly associated with MPD. Green tobacco sickness and pesticide poisoning have symptoms that overlap and symptoms common to other diseases, such as heat-related illness. Heat illness also can produce symptoms such as dizziness, fatigue, muscle cramps, sweating, nausea and others (CDC, 2013). On the other side, heat can increase the absorption of nicotine and pesticides, expanding the effects from these forms of poisoning. Such morbidities self-reported by workers may therefore generate misclassification. Nevertheless, the magnitude of the effect and the dose-response relation reinforce the associations found.

This result appears to indicate that acute nicotine poisoning may have chronic effects on the mental health of tobacco plantation workers, regardless of exposure to pesticides or to other determinants of MPD. Although nicotine has stimulating clinical effects comparable to antidepressant drugs (Vazquez-Palacios et al., 2010), recent studies have confirmed a U-shaped association between intense nicotine consumption and increased symptoms of depression (Hurley and Tizabi, 2013; Ashor, 2013). The possibility also exists that temporary periods of time off work owing to acute GTS may lead to mental disorders arising from nicotine abstinence.

The fact of smoking not having shown association with MPD is consistent with the idea that nicotine association with MPD is U-shaped (Andrade et al., 2013), indicating that lower levels of nicotine exposure may have a different effect than under intense exposure. Nevertheless, among the spouses of pesticide applicators (in AHS) association was found between smoking and depression (Beseler et al., 2006), whereas among pesticide applicators this association was unstable and varied depending on the model (Beseler et al., 2008).

The occurrence of pesticide poisoning episodes is an indicator of intense exposure to these products. This association is well established and is in agreement with several publications (London et al., 2005, 2012; Stallones and Beseler, 2002; Faria et al., 1999; Wesseling et al., 2010; Beseler et al., 2006, 2008; Poletto and Gontijo, 2012; Keifer and Firestone, 2007).

The study assessed the use of PPE when handling pesticides. However, some tobacco growers also used PPE when harvesting, thus making it difficult to distinguish between situations of PPE use. Overwhelmingly, the PPE used most often was inappropriate for both situations or the technical recommendations for its use were not followed. Therefore PPE was not assessed in this article.

This study has provided a detailed characterization of pesticide exposure. As such, in addition to reinforcing the evidence of association between pesticide poisoning and mental health problems, it also points to the increased risk of exposures through dermal contact and exposures to organophosphates. The study also demonstrates that intense nicotine exposure is a potential risk to workers' mental health. Assessing multi-chemical exposure continues to be a challenge and, as such, strategies for characterizing pesticide exposure need to be enhanced. The association between nicotine exposure and MPD needs to be assessed in future studies. Given the overlap of symptoms, new approaches need to be developed in order for researchers and health professionals to be able to distinguish more clearly between pesticide poisoning, nicotine poisoning and heat-related illness.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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### Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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