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Recent pesticide exposure affects sleep: A cross-sectional study among smallholder farmers in Uganda

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ABSTRACT

Background: Poorly educated smallholder farmers in low-income countries are highly exposed to pesticides. This can result in adverse mental health issues, of which sleep problems might be an underlying indicator. We aim to examine the association between sleep problems and pesticide exposure among smallholder farmers in Uganda.
Methods: A cross-sectional survey with 253 smallholder farmers was conducted between October and December 2019. Sleep problems were assessed during the week before the visit using the Medical Outcomes Study Sleep Scale (MOS-SS). Exposure to pesticides was assessed as application days of any pesticide and as use of 2,4-D, glyphosate, mancozeb, organophosphates & carbamates, pyrethroids and other pesticides during the week and year prior to the visit. Associations were assessed using adjusted multivariable logistic regression models.
Results: Increased odds ratio (OR) for the sleep problem index 6-items (OR [95% Confidence Interval] 1.99 [1.04; 3.84] and 3.21 [1.33; 7.82]), sleep inadequacy (1.94 [1.04; 3.66] and 2.49 [1.05–6.22]) and snoring (3.17 [1.12; 9.41] and 4.07 [1.04; 15.14]) were observed for farmers who respectively applied pesticides up to two days and three or more days in the past week compared to farmers who did not apply during the past week. Gender-stratified analyses showed a higher OR for female applicators (4.27 [1.76–11.16]) than for male applicators (1.82 [0.91–3.79]) for the association between the sleep problem index 6-items and pesticide use in the week before the visit. Increased ORs were also observed for the association between the sleep problem index 6-item and mancozeb exposure during the past year 2.28 [1.12–4.71] and past week 2.51 [0.86–7.55] and glyphosate exposure during the past week 3.75 [1.24–11.8] compared to non-applicators.
Discussion: Our findings suggest an increased risk of sleep problems among smallholder farmers in a pesticide-exposure-dependent way in a low-income context. Further gender-stratified, longitudinal investigations are warranted to confirm these findings.

1. Introduction

Pesticides are widely used to control and prevent pests in households and agriculture (Pretty and Bharucha, 2015). In high-income countries, human exposure to pesticides has been minimized to low levels by the implementation of control measures and regulations (Handford et al., 2015). However, in low- and middle-income countries (LMICs), implementation and enforcement of legislation are often inadequate (Mengistie et al., 2017). Furthermore, pesticide knowledge, attitude, and practices are often insufficient among low educated agricultural communities, leading to extremely high exposure profiles in farmers and farmworkers (Staudacher et al., 2020). Exposure to pesticides has been associated with various neurological health effects, including acute and chronic neurological symptoms (e.g., sleep problems or headache) (Farnham et al., 2021), neurobehavioural problems (e.g., impaired memory or reaction speed) (Fuhrimann et al., 2021) or mental health issues (e.g., increased level of depression or anxiety) (Yazd et al., 2019).

A wide range of currently used pesticides are endocrine-disrupting or

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neurotoxic (Jepson et al., 2020). Exposure to organophosphate (OPs) and carbamates insecticides inhibit acetylcholinesterase (AChE) and therewith disturb the serotonergic system (Judge et al., 2016). Low-level exposure to AChE inhibiting pesticides was shown to be associated with depression and anxiety (Harrison and Mackenzie Ross, 2016) and an increased risk for suicidality (London et al., 2005). Other insecticides, such as pyrethroids, which act on voltage-gated sodium channels in neurons, have also been found to be associated to psychological disorders (Costa et al., 2008; London et al., 2012; Lucero and Muñoz-Quezada, 2021). Exposure to the widely used herbicide glyphosate has been linked to impaired visual memory (Fuhrimann et al., 2021), and exposure to the manganese-containing fungicide mancozeb was shown to be associated with thyroid disorders (Leemans et al., 2019) and neurodevelopmental disorders (van Wendel de Joode et al., 2016).

Sleep problems are an underlying indicator of mental health issues, most frequently for depression (Khan et al., 2019; Tsuno et al., 2005). Several studies have indicated that 50–90% of people with diagnosed depression also report sleep problems. This association has also been validated in low-income countries (Stickley et al., 2019). Moreover, increased risks for a broad range of psychiatric distress symptoms were found for individuals with comorbidity of sleep problems and depression compared to sleep problems alone. However, little is known about the effects of pesticide exposure on sleep. Occupational exposure was associated with sleep problems in a study with greenhouse farmworkers in China (Li et al., 2019) and with sleep behavior disorder in a multinational study (Postuma et al., 2012), while non-occupational pesticide exposure was reported to be linked to sleep behavior disorder in a cohort in China (Zhang et al., 2020). However, these studies did not discriminate between the wide range of pesticide groups or active ingredients used. Other reports indicate associations of occupational exposure to OPs (Farahat et al., 2003; Jamal et al., 2016) and pyrethroids with fatigue (Bradberry et al., 2005) and dream enacting behaviors (Shrestha et al., 2018). Hence, knowledge on the association between multiple pesticides currently used in agriculture is missing, especially from contexts in LMICs, where pesticide exposure is highest.

The aim of the current study was to investigate the association between sleep problems and pesticide exposure among smallholder farmers in Uganda. The two specific objectives were to examine the association between sleep problems and: (i) weekly number of application days of any pesticide; and (ii) the weekly and yearly use of specific active ingredients.

2. Methods

2.1. Ethical considerations

The Higher Degrees, Research and Ethics Committee of Makerere University School of Public Health approved this study (reference no. 719). The objectives of the study were explained to all participants, and written informed consent was obtained. A modest non-prior communicated refreshment was offered to every respondent at the end of the interview as compensation for their time.

2.2. Study area and population

This cross-sectional study was conducted in the rural Sub Counties of Mende and Masulita inWakiso District, Central Region of Uganda. Smallholder farmers (farms with $<$ 2 ha) in this area predominantly grow beans, maize, sweet potatoes, banana, cassava, coffee, tomatoes, and groundnuts (Diemer et al., 2020; Staudacher et al., 2020). While pesticide use is increasing within these smallholder systems, leading to profound environmental contamination (Fuhrimann et al., 2020a), applicators are mostly not trained on safe practices and have shown poor knowledge, attitude and practice (KAP) of safe pesticide handling, which can result in high exposure due to from example inadequate use of personal protective equipment (Staudacher et al., 2020).

Participants (18 years or older) were recruited from a cohort of 302 smallholder farmers, which was established during the Pesticide Use in Tropical Settings Project (PESTROP) in 2017 (Fuhrimann et al., 2019). In brief, to establish the initial cohort in 2017, organic (using fewer pesticides) and conventional farmers were recruited to ensure a certain pesticide exposure contrast. Further, organic farmers were recruited through snowball sampling and conventional farmers through a list provided by local village chairpersons, followed by random clustered convenience sampling (Diemer et al., 2020; Staudacher et al., 2020). The follow-up survey in 2019 was linked to the "Improving exposure assessment methodologies for epidemiological studies on pesticides" (IMPRESS) project, which took place also in the UK and Malaysia (Galea et al., 2019; Jones et al., 2020). In the follow-up in Uganda, the participants were invited to a face-to-face workshop, during which they were informed about the proposed study's nature, objectives, and benefits/risks, as well as updating their mobile phone contacts and home addresses. This was then followed by phone calls to share the schedule and set up appointments for individual interviews.

2.3. Data collection

Data were collected using structured questionnaire interviews between October and December 2019. The questionnaire was previously developed, adapted, and used in different contexts in LMICs, including a survey with the same study population in 2017 (Fuhrimann et al., 2021, 2019; Hansen et al., 2021, 2020; Staudacher et al., 2020). The questionnaire included questions on sociodemographic characteristics (e.g., sex, age, education, household income), potential confounders (e.g., alcohol consumption), self-reported pesticide use over the past week and year, and self-reported sleep problems over the past week. Interviews were administered in the local language of Luganda by six trained research assistants via tablet computer devices using "Open Data Kit", an open-source software for collecting and exporting datasets (https://opendatakit.org). Over two weeks, investigators received training on tools, ethics, and research background. Additionally, we conducted a week-long pilot study. Interviews were held at home and/or in the field, and were appropriately scheduled to cause minimal disruption to farmers' activities, before and after the working in the fields.

2.4. Pesticide exposure assessment

Exposure to pesticides was defined as the number of days the participant had applied pesticides on their crops, livestock, or household in the seven days prior to the interview. With the help of a cheat sheet indicating the days of the week the participants were asked if they had used pesticides, starting at yesterday until seven days ago. Later they were grouped into three strata based on the distribution of our data: non-user; applied during one or two days; and applied more than two days.

To obtain information about the use of different active ingredients in the past week and year, participants were asked about brand names of 53 pesticide products which were listed on a cheat sheet (Supplementary information (SI) Table S1) and registered by Uganda's Ministry of Agriculture Animal Industry and Fisheries including a total of 15 pesticide active ingredients (Fuhrimann et al., 2021; Staudacher et al., 2020). In addition, participants were asked if they had used any other pesticide product, which was not mentioned by the investigator. Mentioned pesticide products were then assessed for active ingredients. For the analysis, active ingredients were assessed in the following six groups: 2,4-D; carbamates and OPs; mancozeb; glyphosate; pyrethroids; and other active ingredients. Each group was looked at in three strata non-user, applied last week and applied last year.

2.5. Sleep outcomes

To measure sleep problems, the Medical Outcomes Study Sleep Scale

(MOS-SS) questionnaire with a 1-week recall period was applied (Hays and Stewart, 1992). The MOS-SS is a 12-items questionnaire to assess key constructs of sleep. Two overall sleep problems indices (6- and 9-items) were calculated, as well as six sleep dimensions (sleep disturbance (4-items), sleep inadequacy (2-items), daytime somnolence (3-items), snoring (1-item), awakening short of breath or with a headache (1-item), and non-optimal sleep quantity (1-item); Table 1).

The MOS-SS measurement period, which is usually 1-month, was adapted to one week to investigate potential acute effects of pesticide exposure. The 1-week recall period showed to be reliable in other studies (Sadosky et al., 2009). For example, as follows: “How often during the past four weeks did you …” was changed to “How many days in the last week did you …”. The original 6-point Likert scale from “not at all” to “all the time” was changed to an 8-point Likert scale from 0 to 7 days. To calculate the indices and dimensions, the number of days reported for each of the questions (0 to 7 days) were proportionally transformed to a scale from 0 to 100, with a high score indicating sleep problems. To dichotomize the score for further analysis, a cut-off value of 30 was used based on the distribution of our data (considered symptomatic). The sleep dimension “non-optimal sleep quantity” (i.e., the average number of hours of sleep per night) was dichotomized by considering seven or eight hours of sleep as “optimal sleep” and less than seven hours or more than eight hours as a non-optimal quantity of sleep.

2.6. Statistical analyses

Median and interquartile range (IQR) were obtained for descriptive analysis of continuous variables, and frequency and percentage for categorical variables. Internal consistency of the sleep problem indices was confirmed using Cronbach’s alpha and the ‘item convergent criterion’ and ‘item discrimination criterion’. We assessed correlations between the two sleep problem indices and six dimensions and the six pesticide active ingredients/chemical groups using Spearman correlation coefficients (r_s).

First, adjusted multivariable logistic regression analyses were performed to investigate the association between eight sleep problem indices and three strata of application days in the past week (i.e., non-user in the past week; applied on one or two days; and applied on more than two days). To reduce chance of false-positive findings (Type I error rates), a second multivariable logistic regression analysis was only performed for the index which was associated in the first model (*p*-values below 0.05; i.e., for 6-item index) with the six active ingredients/chemicals groups during the past year and week prior to the study visit (i.e., non-user, applied last week and applied last year).

All regression analyses were adjusted for the following covariates (selected *a priori* based on previous studies that examined occupational pesticide exposure and sleep outcomes (Baumert et al., 2018; Li et al., 2019)): age (split in tertiles: ≤44, 45–57, and ≥ 58 years), sex, alcohol consumption (non-current drinker *vs* current drinker), body mass index (BMI; < 18.5, 18.5 – 24.9 and ≥ 25.0), and sleep disruption during the past week (no *vs.* yes). BMI was based on weight and height measured from the PESTROP survey in 2017 (Fuhrimann et al., 2019; Winkler et al., 2019). Sleep disruption was indicated when participants reported being disrupted during their sleep in the past week due to six distinct reasons (mosquitos, bedbugs, noise, suffering from an infectious disease, wearing an actimeter (which part of a parallel study), or any other reason due to which their sleep was impacted).

Two sensitivity analyses following the initial multivariable logistic regression analyses were performed: (i) Gender-stratified analyses due to known differences in sleep patterns, due to the low-sample size of women who sprayed more than two times last week (n = 3), the model used only two exposure strata (not sprayed pesticides last week and sprayed pesticides last week)). (Hajali et al., 2019; Mong and Cusmano, 2016; Shaib and Attarian, 2017); and (ii) the underlying six questions/items were also analysed separately. Across all analyses, *p*-values below 0.05 were considered statistically significant. Statistical analyses were

Table 1
Overview of the Medical Outcomes Study Sleep Scale (MOS-SS) two sleep indices (6- and 9-items) and six sleep dimensions and the corresponding 12 individual questions/items.

	Questions											
	1 Time to fall asleep	2 Sleep quantity	3 Sleep restlessness	4 Enough sleep, feel rested upon waking	5 Awakening short of breath or headache	6 Feel drowsy during the day	7 Trouble falling asleep	8 Awaken during sleep	9 Trouble staying awake during day	10 Snore during sleep	11 Taking naps during the day	12 Amount sleep needed (hours)
Sleep problems index												
6-items				x	x		x	x	x			x
9-items	x		x	x	x	x	x	x	x			x
Dimensions												
Sleep disturbance	x		x				x	x				
Daytime somnolence						x			x		x	
Sleep inadequacy				x								x
Snoring										x		
Awakening short of breath or headache					x							
Non-optimal sleep quantity		x										

conducted in R (Foundation for Statistical Computing, version 3.6.3, RStudio version 1.2).

3. Results

3.1. Sociodemographic of the study population

Out of 302 farmers who initially participated in the PESTROP survey, 256 participants could be enrolled in the follow-up and 253 were eligible for the analysis in this study (Figure S2). Most of the study participants were male (59%), finished primary school (67%), did not consume alcohol (70%) and had a normal BMI (18.5–24.9, 66%) (Table 2). Median (interquartile range (IQR)) age was 52 (19) years, while about a third (32 %) of the farmers had a average household income of less than one USD per month.

3.2. Pesticide use

About half of the 253 farmers (47%) reported they applied pesticides during the week preceding the interviews (Table 2). A third (34%) applied during one or two days and 13% applied more than two days. Most of the applicators were men (78%) and belonging to the youngest age groups (≤39; 44%), and were subjects with normal BMI.

Over the year before the visit, 30 different active ingredients were reported to be used (Table 3 and Table S3). Glyphosate was most frequently used (60%), followed by pyrethroids (49%; consisting of five different active ingredients), mancozeb (40%), carbamates and organophosphates (35%; consisting of nine different active ingredients), 2,4-D (29%), and other active ingredients (15%; consisting of 13 active ingredients and 32 farmers who did not know the name of the pesticide product). We observed at maximum moderate correlations between farmers who applied last year and applied last week of glyphosate and 2,4-D (r_s 0.46) and between OPs and carbamates and cypermethrin (r_s 0.49) (Table S4).

3.3. Sleep outcomes

The highest prevalence among the eight sleep problem indices was non-optimal sleep quantity (hours) (62%), followed by sleep inadequacy and the 6-items sleep problem index (Table 4). In addition to the eight sleep indices, three quarters of the participants (75%) reported that their sleep was disturbed due to outside factors (Table 2). Most prominently by mosquitos (44%), followed by noise (26%), bedbugs (19.0%) and suffering from an infectious disease during the assessment week.

3.4. Logistic regression of pesticide use with the sleep problem indices and dimensions

Increased odds for the sleep problem index 6-item (Odds Ratio [95% Confidence Interval] of 1.99 [1.04; 3.84] and 3.21 [1.33; 7.82]), sleep inadequacy (1.94 [1.04; 3.66] and 2.49 [1.05–6.22]) and snoring (3.17 [1.12; 9.41] and 4.07 [1.04; 15.14]) were observed for farmers who applied pesticides up to two days and three or more days in the past week compared to non-applicators; Table 5). For the 9-item index and the other four dimensions, null associations were observed for increased exposure.

Increased odds were also observed for the association between the 6-item sleep problem index and mancozeb exposure during the past year (2.28 [1.12–4.71]) and past week (2.51 [0.86–7.55]) and glyphosate exposure during the past week (3.75 [1.24–11.8]; Table 6) compared to non-applicators. For the other four assessed specific active ingredients/ chemical groups null associations were observed for increased exposure.

3.5. Sensitivity analysis

Gender-stratified analyses showed higher odds for female applicators (4.27 [1.76–11.16]) than for male applicators (1.82 [0.91–3.79]) for the association between the sleep problem index 6-item and pesticide use in the week before the visit; Table S5). Among the 6-item sleep problem index underlying questions, the "amount of sleep needed" was associated with higher odds for individuals who applied pesticides on one or

Table 2
Socio-demographic characteristics of farmers in Wakiso, Uganda, 2019 [n (%)].

Characteristics		All farmers	Non-applicators**	Applicators (1 or 2 days)	Applicators (>2 days)
All farmers		253 (1 0 0)	135 (1 0 0)	86 (1 0 0)	32 (1 0 0)
Sex	Male	149 (58.9)	56 (41.5)	64 (74.4)	29 (90.6)
	Female	104 (41.1)	79 (58.5)	22 (25.6)	3 (9.4)
Age (years)	≤ 39	85 (33.6)	33 (24.4)	39 (45.3)	13 (40.6)
	40–49	86 (34)	40 (29.6)	34 (39.5)	12 (37.5)
	≥ 50	82 (32.4)	62 (45.9)	13 (15.1)	7 (21.9)
Finished primary school	No	84 (33.2)	41 (30.4)	28 (32.6)	25 (46.9)
	Yes	169 (66.8)	94 (69.6)	58 (67.4)	17 (53.1)
Household income per month	< 1 USD	79 (31.5)	50 (37.0)	24 (27.9)	5 (13.2)
	≥ 1 USD	159 (62.9)	75 (55.6)	56 (65.1)	27 (71.1)
	Missing#	22 (8.8)	10 (7.4)	6 (7.0)	6 (15.8)
Currently consuming alcohol	No	178 (70.4)	102 (75.6)	52 (60.5)	24 (75)
	Yes	75 (29.6)	33 (24.4)	34 (39.5)	8 (25)
BMI	Normal (18.5–24.9)	167 (66)	79 (58.5)	64 (74.4)	24 (75)
	Low (<18.5)	14 (5.5)	6 (4.4)	5 (5.8)	3 (9.4)
	High (≥25.0)	72 (28.5)	50 (37)	17 (19.8)	5 (15.6)
Sleep disruption during assessment week*	No	64 (25.3)	35 (25.9)	21 (24.4)	8 (25)
	Yes	189 (74.7)	100 (74.1)	65 (75.6)	24 (75)
Underlining reasons for sleep disruption					
Mosquitos		111 (43.9)	64 (47.4)	36 (41.9)	11 (34.4)
Bedbugs		48 (19.0)	26 (19.3)	17 (19.8)	5 (15.6)
Noise		66 (26.1)	30 (22.2)	25 (29.1)	11 (34.4)
Infectious disease		45 (17.8)	28 (20.7)	12 (14.0)	5 (12.5)
Wearing activity meter		7 (2.8)	0 (0)	3 (3.5)	4 (12.5)
Other reasons		69 (33.0)	33 (24.4)	27 (31.4)	9 (28.1)

BMI: Body Mass Index; #Missing values as farmers were not willing to report their income; *Sleep disruption variable consist of six reasons for sleep disruption. **farmers who did not apply pesticides in the week before the study visit.

Table 3
Use of active ingredients in the year and the year and week before the study visit, stratified in six chemical groups which were used in the logistic regression models [n (%)].

Chemical groups	Type	Active ingredients*	Last year	Last week
Alkylchlorophenoxy	Herbicide	2,4-D	63 (24.9)	10 (4)
Phosphonoglycerine	Herbicide	Glyphosate	120 (47.4)	31 (12.3)
Dithiocarbamates	Fungicide	Mancozeb	70 (27.7)	32 (12.6)
Organophosphates & carbamates	Insecticides	Profenofos, ChlorpyrifosDichlorvos, Dimethoate, Diazinon, Propamocarb hydrichlorideCarbaryl, Carbofuran, Carbendazim	55 (21.7)	33 (13)
Pyrethroids	Insecticides	Cypermethrin, Lambda-Cyhalothrin, Deltamethrin, Permethrin and Tetramethrin	82 (32.4)	41 (16.2)
Others*	Various	15 different active ingredients	14 (5.5)	25 (9.9)
Spraying any active ingredients			78 (30.8)	118 (46.6)

*Yearly and weekly use of 14 different active ingredients are listed in the supplementary information Table S3.

Table 4
Showing eight sleep problem indices stratified in non-applicators and applicators who sprayed one or two times and more than two times during the week before the visit.

Sleep problems indices	All farmers (n 253)		Non-applicators (n 135)		Applicators 1 or 2 days (n 86)		Applicators > 2 days (n 32)	
	Cases n (%)	Median (IQR)	Cases n (%)	Median (IQR)	Cases n (%)	Median (IQR)	Cases n (%)	Median (IQR)
6-items	90 (36)	21 (26)	39 (29)	17 (29)	35 (41)	23 (29)	16 (50)	30 (23)
9-items	79 (31)	22 (23)	39 (29)	19 (25)	30 (35)	23 (21)	10 (31)	24 (20)
Sleep disturbance	57 (23)	13 (29)	30 (22)	10 (28)	20 (23)	19 (25)	7 (22)	6 (27)
Sleep inadequacy	142 (56)	43 (71)	68 (50)	36 (71)	53 (62)	50 (57)	21 (66)	64 (73)
Daytime somnolence	78 (31)	14 (29)	44 (33)	14 (31)	23 (27)	17 (29)	11 (34)	19 (27)
Snoring	26 (10)	0 (0)	10 (7)	0 (0)	11 (13)	0 (0)	5 (16)	0 (0)
Awakening short of breath or headache	13 (5)	0 (0)	8 (6)	0 (0)	4 (5)	0 (0)	1 (3)	0 (0)
Non-optimal sleep quantity (hours)	157 (62)	6 (3)	76 (56)	7 (3)	60 (70)	6 (2)	21 (66)	6 (2)

Table 5
Multivariable logistic regression analysis of the eight and their association with unspecific number of pesticide use days in the week before the study visit.

Sleep problems indices/dimensions	Days spraying last week#	Adjusted OR (95% CI)##	*p*-value
Sleep problem indices			
9-items	0	1	
	1 and 2	1.39 (0.72–2.69)	0.327
	> 2	1.22 (0.48–2.99)	0.670
6-items	0	1	
	1 and 2	1.99 (1.04–3.85)	0.038*
	> 2	3.21 (1.33–7.82)	0.009**
Sleep problem dimensions			
Sleep disturbance	0	1	
	1 and 2	0.91 (0.43–1.9)	0.807
	> 2	0.9 (0.3–2.48)	0.848
Sleep inadequacy	0	1	
	1 and 2	1.94 (1.04–3.66)	0.038*
	> 2	2.49 (1.05–6.22)	0.043*
Daytime somnolence	0	1	
	1 and 2	0.7 (0.35–1.36)	0.295
	> 2	0.93 (0.37–2.24)	0.865
Snoring	0	1	
	1 and 2	3.17 (1.12–9.41)	0.032*
	> 2	4.07 (1.04–15.14)	0.036*
Awakening short of breath or headache	0	1	
	1 and 2	0.63 (0.15–2.36)	0.503
	> 2	0.44 (0.02–2.94)	0.469
Non-optimal sleep quantity (hours)	0	1	
	1 and 2	1.46 (0.76–2.83)	0.260
	> 2	0.9 (0.37–2.25)	0.820

*p-value below 0.05; **p-value below 0.01; #reference 1, non-sprayers during the week prior to the study visit; ##model adjusted for sex, age, currently consuming alcohol, body mass index, and sleep disturbance during the past week; Ad. OR: adjusted Odds Ratio; CI: confidence interval.

Table 6
Multivariable logistic regression analysis of the 6-items and its association with six active ingredients/pesticide groups in the year and week before the study visit.

Active ingredients/Chemical group	User	Adjusted OR (95% CI)	p-value
2,4-D	Non-user	1	
	Last year	0.92 (0.44–1.87)	0.81
	Last week	0.84 (0.16–4.61)	0.84
Glyphosate	Non-user	1	
	Last year	1.29 (0.64–2.59)	0.48
	Last week	3.75 (1.24–11.8)	0.02*
Mancozeb	Non-user	1	
	Last year	2.28 (1.12–4.71)	0.02*
	Last week	2.51 (0.86–7.55)	0.09*
Organophosphates and carbamates	Non-user	1	
	Last year	0.7 (0.33–1.45)	0.35
	Last week	0.5 (0.16–1.48)	0.22
Pyrethroids	Non-user	1	
	Last year	1.33 (0.67–2.64)	0.41
	Last week	1.64 (0.55–4.94)	0.37
Other active ingredients	Non-user	1	
	Last year	1.31 (0.38–4.36)	0.66
	Last week	0.86 (0.29–2.51)	0.79

*p-value below 0.05; #reference 1, non-sprayer during the year prior to the study visit; ##model adjusted for sex, age, currently consuming alcohol, body mass index, and sleep disturbance during the past week; Ad. OR: adjusted Odds Ratio; CI: confidence interval

two days (1.99 [1.04; 3.84]) and on three or more days in the past week (3.21 [1.33; 7.82]; Table S6).

4. Discussion

We examined the association between reported sleep problems using a validated method (MOS-SS) and pesticide use during the past week and the past year among smallholder farmers in Uganda. We showed an exposure-dependent effect on self-reported sleep problems with increasing number of application days over one week and with somewhat higher odds among female applicators. In addition, only participants applying glyphosate in the week before our study visit were more likely to experience sleep problems. Participants applying mancozeb were more likely to report sleeping problems irrespective of whether they applied it in the week or the year prior to the visit.

The exposure-dependent effect of the number of application days with the sleep problem index 6-items is in line with a study conducted by Li et al. (2019). The effects found for snoring have been reported in studies of pesticide exposure on respiratory health (Amoatey et al., 2020; Hansen et al., 2021; Negatu et al., 2017). Snoring is also a sign of sleep apnea (Li et al., 2016). Baumert and colleagues (2018) found an increased risk for sleep apnea after low-level exposure to carbamates among US farmers. This can be explained by the acetylcholinesterase inhibiting properties of OPs and carbamates (including mancozeb) and leading to respiratory depression (i.e., hypoventilation) (Colovic et al., 2013). Despite this, no effect was found for the item ‘awakening short of breath or with a headache. Sleep problems are an underlying indicator for psychological symptoms and adults in low-income countries who experience sleep problems are up to 3.6 times more likely to experience depressive symptoms (Khan et al., 2019; Tsuno et al., 2005).

The shown adverse effect due to chronic (last year) and acute (last week) exposure of mancozeb on sleep might be explained by the action of the metabolite ethylenethiourea on the thyroid, leading to a disruption of thyroid functioning (Costa et al., 2008; Leemans et al., 2019; Richardson et al., 2019). An underactive thyroid (hypothyroidism) may impact sleep. Moreover, manganese and ethylenethiourea found in infants because of prenatal exposure to mancozeb have been associated with impaired neurodevelopment (van Wendel de Joode et al., 2016), which is an indication for its neurotoxic properties.

The acute effect found for the herbicide glyphosate is in line with animal studies which suggested neurotoxic effects of glyphosate and glyphosate-based herbicides, including depressive behavior (Ait Bali et al., 2017; Cattani et al., 2017). To date, only a few case studies suggesting that acute glyphosate exposures may lead to direct cerebral toxicity (Malhotra et al., 2010; Potrebić et al., 2009; Wang et al., 2011). A recent analysis of neurobehavioral outcomes, collected within the same PESTROP study collective in 2017, showed an association between glyphosate exposure and impaired visual memory (Fuhrimann et al., 2021). Further, a case-control study found that prenatal residential proximity to agricultural glyphosate applications was associated with increased odds of autism spectrum disorder (ASD) during childhood (Von Ehrenstein et al., 2019). However, besides this recent evidence on glyphosate from epidemiological surveys, there is a lack of real-world exposure data and related health outcomes, and insight in its neurotoxic potential (Landrigan and Belpoggi, 2018). This is concerning as the broad-spectrum herbicide glyphosate is the most widely used herbicide in Uganda and globally (Benbrook, 2016).

Contrarily, no effect was found for pesticide groups like OPs, carbamates (other than mancozeb), and pyrethroids which are known to also affect the thyroid system and lead to neurological symptoms (Leemans et al., 2019). These null findings have to be interpreted with caution as in our regression models several insecticide active ingredients are classified under these groups (nine active ingredients for OPs and carbamates and five active ingredients for pyrethroids) and farmers' actual exposure will be different to mixtures of these active ingredients. Also, some insecticides are often used together in the same pesticide product in our study population (e.g., profenofos (OP) and cypermethrin (pyrethroids) applied by 57 farmers and chlorpyrifos (OP) and cypermethrin applied by 30 farmers).

5. Strengths and limitations

The present study had three considerable strengths (i) frequency of use over the past week was recorded using a cheat sheet to report daily use of pesticide products in a low-educated population in a low-income setting in Uganda; (ii) an assessment could be made of 30 different active ingredients and six distinct active ingredients/chemical groups could be investigated; and (iii) gender stratified analyses were performed, elucidating that women seemed to be more prone to the effects of pesticide exposure on sleep.

There are three limitations worth mentioning: (i) the findings are based on a cross-sectional study design which limits its causal interpretation. Therefore, pesticide-related sleep problems should be further investigated in longitudinal studies; (ii) despite we adjusted for several potential confounders, we cannot exclude the possibility of residual confounding. There are important confounders, which could affect sleep that we could not investigate in full detail with our questionnaire tool (e.g., housing condition, socioeconomic status, lifestyle or medical status); and (iii) our study might be prone to recall bias as we relied on self-reported use of pesticides and sleep outcomes. To validate self-reported use of pesticides, one could collect biomonitoring data (Atabila et al., 2018) or use exposure intensity-scores based on context-specific exposure algorithms (Fuhrimann et al., 2020b) to account for differences in pesticide handling during an application day (e.g., different mixing/application techniques, amount used, personal protective devices and hygienic behavior). Also, prolonged (dermal) exposure after an application should be incorporated and evaluated (e.g., due to re-entry work or poor hygienic practices). The self-reported sleep problems could be objectified by using activity meters or by using polysomnography to determine the quality of sleep.

6. Conclusions

Our findings suggest increased sleep problems among smallholder farmers in a pesticide-application frequency-dependent way in a low-income context. Indeed, sleep disorders are critical in these vulnerable smallholder communities, as their general well-being and productivity could be impacted, which adds another burden to these disadvantaged and poor communities. The findings concerning women show even higher increased odds for affected sleep with a lower frequency of application. The associations between the widely used fungicide mancozeb and herbicide glyphosate and sleep problems should be further investigated in short- and long-term longitudinal studies. Finally, context-specific control measures should be developed to minimize pesticide exposure in smallholder communities.

Author contributions

SF, AA, PS and HK: conzeptulization and funding acquisation. SF, AA, IvB: collection of data. SF, LP, IvB, HK: analysis, visualization and interpretation of data. IvB and SF: writting - original draft . All authors participated in editing the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106878.

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