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Association of activities related to pesticide exposure on headache severity and neurodevelopment of school-children in the rural agricultural farmlands of the Western Cape of South Africa

Shala Chetty-Mhlanga[a,b,c], Samuel Fuhrimann[d], Wisdom Basera[a], Marloes Eeftens[b,c], Martin Röösli[b,c,*], Mohamed Aqiel Dalvie[a]

[a] Centre for Environment and Occupational Health Research, School of Public Health and Family Medicine, University of Cape Town, South Africa
[b] Swiss Tropical and Public Health Institute, Basel, Switzerland
[c] University of Basel, Switzerland
[d] Institute for Risk Assessment Sciences (IRAS), Utrecht University, 3584 Utrecht, Netherlands

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ABSTRACT

Objective: Children and adolescents living in agricultural areas are likely to be exposed to mixtures of pesticides during their daily activities, which may impair their neurodevelopment. We investigated various such activities in relation to headache severity and neurodevelopment of school-children living in rural agricultural areas in the Western Cape of South Africa.
Method: We used baseline date from 1001 school-children of the Child Health Agricultural Pesticide Cohort Study in South Africa (CapSA) aged 9–16 from seven schools and three agriculture areas in the Western Cape. Questionnaires were administrated to assess activities related to pesticide exposure and health symptoms addressing four types of activities: 1) child farm activities related to pesticide handling, 2) eating crops directly from the field, 3) contact with surface water around the field, and 4) seen and smelt pesticide spraying activities. Neurocognitive performance across three domains of attention, memory and processing speed were assessed by means of an iPad-based cognitive assessment tool, Cambridge Automated NeuroPsychological Battery (CANTAB). Headache severity was enquired using a standard Headache Impact Test (HIT-6) tool. Cross-sectional regression analysis was performed.
Results: About 50% of the cohort report to have ever been engaged in activities related to pesticide exposure including farm activities, eating crops directly from the field and leisure activities. Headache severity score was consistently increased in relation to pesticide-related farm activities (score increase of 1.99; 95% CI: 0.86, 3.12), eating crops (1.52; 0.41, 2.67) and leisure activities of playing, swimming or bathing in nearby water (1.25; 0.18, 2.33). For neurocognitive outcomes, an overall negative trend with pesticide exposure-related activities was observed. Among others, involvement in pesticide-related farm activities was associated with a lower multitasking accuracy score (−2.74; −5.19, −0.29), while lower strategy in spatial working memory (−0.29; −0.56; −0.03) and lower paired associated learning (−0.88; −1.60, −0.17) was observed for those who pick crops off the field compared to those who do not pick crops off the field. Eating fruits directly from the vineyard or orchard was associated with a lower motor screening speed (−0.06; −0.11, −0.01) and lower rapid visual processing accuracy score (−0.02; −0.03, 0.00).
Conclusions: Children who indicate activities related to pesticide exposure may be at higher risk for developing headaches and lower cognitive performance in the domains of attention, memory and processing speed. However, self-reported data and cross-sectional design are a limitation. Future research in CapSA will consider pesticide exposure estimations via urinary biomarkers and longitudinal assessment of cognitive functions.

Abbreviations: CapSA, Child Health Agricultural Pesticide Cohort Study in South Africa; CANTAB, Cambridge Automated NeuroPsychological Battery; HIT-6, Headache Impact Test; LMICs, Low- and Middle-Income Countries.

* Corresponding author at: Swiss Tropical and Public Health Institute, Basel, Switzerland.
E-mail addresses: sh.mhlanga@swisstph.ch (S. Chetty-Mhlanga), s.fuhrimann@uu.nl (S. Fuhrimann), marloes.eeftens@swisstph.ch (M. Eeftens), martin.roosli@swisstph.ch (M. Röösli), aqiel.dalvie@uct.ac.za (M.A. Dalvie).

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1. Background

Children living in agricultural areas are likely to be exposed to various neurotoxic pesticides during their daily lives. The most vulnerable populations are the farmworkers and families in low- and middle-income countries (LMICs) (Fenske et al., 2000). Children are expected to be more vulnerable to environmental exposure than adults due to their still developing organs and higher dermal contact including: hand-to-mouth activities, larger food intake per unit height and body weight, breathing in relatively larger volumes of air, and playing in more hazardous zones for example in outdoor activities with closer contact to the ground (Fenske et al., 2000; Bellinger, 2018). Neurodevelopmental disorders linked to early exposures of pesticides include Autism (Sagiv Sharon et al., 2018), Attention Deficit Hyperactivity Disorder (ADHD) (Yu et al., 2016), poorer social behavior, lower Intelligence (IQ) and worse behavioral regulation (Furlong et al., 2017; Gonzalez-Casanova et al., 2018). The majority of evidence has focused on pre-natal exposure to pesticides and the effect on neurodevelopment of children up to seven years old since the developing brain is most vulnerable at this stage to all three processes of development including building neurons, synaptology and mylenation (Bellinger, 2018; Abdel Rasoul et al., 2008). However, older children and adolescents in rural areas engage in work and leisure time activities and thus may be exposed to relatively high pesticide levels. Although less studied, they are vulnerable to chronic health symptoms as recently observed in two cohorts of adolescents working as pesticide applicators in Egypt with consequent neurobehavioral deficits in processing speed, attention, memory and neurological symptoms (Ismail et al., 2017).

Children and adolescents are thus exposed to a mixture of different pesticides (Dalvie et al., 2011; English et al., 2012). Organophosphates (OPs) are widely used for outdoor application, but are also used indoors for pesticide control (Fenske et al., 2000). OP's, specifically Chlorifyros, affects the brain in both an acutely toxic manner, irreversibly inhibiting the Acetacholenestraasse (ACHE) to break down the neurotransmitters, but at the same time, chronic exposure to this pesticide may also interfere with the brain at less severe structural processes (Li et al., 2019). A recent study on post-natal exposure to low-level Chlorpyrifos in children confirms the inhibition of cholinesterases (CHe) through an alternate target compared to that of high dose exposure on CHe inhibition (Perez-Fernandez et al., 2020). A similar study on rats confirmed this distinction, revealing that compared to the acute high-dose exposure to the OP Malathion effect inhibiting AChE activity; long-term exposure effected the Spatial Working Memory of rats (dos Santos et al., 2016). Additionally, the association of headache symptoms to occupational OP exposure in children are suggestive of the consequential chronic effects of pesticides on the nervous system (Rastogi et al., 2010).

South Africa, an upper middle-income country has the highest application rates of pesticides in Sub-Saharan Africa (Quinn, et al., 2011). Over 3000 different types of pesticide product formulations are registered, including the possible neurotoxic and endocrine disrupting chemicals (EDCs) active ingredients bifenthrin, chlorpyrifos, cypermethrin and mancozeb (Dabrowski, 2015; DAFF, 2010). In the Western Cape, a wide range of pesticides have been detected in the environment and in exposed persons, whose modes of uptake and level of toxicity are very different (Fuhrimann et al., 2020; Curchod et al., 2020; Dalvie et al., 2003; Dalvie et al., 2009). A recent study in the Western Cape in 2017, showed that the dominating stone fruit, grapes and wheat farms used up to 96 active ingredients (47 fungicides, 31 insecticides and 18 herbicides). Most common active ingredients which were used include 2,4-d, bromoxynil, chlorpyrifos, glyphosate, mancozeb, MCPA, penconazole, spiroxamine. This intensive farming system in the Western Cape also lead to environmental contaminants. For example, levels of pesticides in surface water that exceeded environmental quality standards (i.e., for imidacloprid, thiacloprid, chlorpyrifos and acetamiprid, terbuthylazine) (Curchod et al., 2020) or the persistent presence of pesticides in ambient air (e.g., atrazine, carbaryl, chlorpyrifos or malathion) (Fuhrimann et al., 2020). In addition, previously banned but environmentally-persistent pesticides such as endosulfan were frequently detected in drinking and surface water (Dalvie et al., 2003; Dalvie et al., 2009). Ultimately human exposure to organophosphates and endosulfan metabolites have also been reported in farm workers and residents of the rural Western Cape (Dalvie et al., 2014; Dalvie et al., 2011). However, there is a lack in human exposure data to pesticide mixtures or assessments of activities which may lead to mixed exposure situations specifically in resident populations.

This study aims at investigating the association between activities related to pesticide exposure, headache and neurocognitive functioning of children and adolescents in three agricultural areas in the Western Cape of South Africa. Our hypothesis is that children who engage with pesticide-related activities, have a higher chronic pesticide exposure and thus lower cognitive functioning and increased health symptoms than those who do not.

2. Methods

2.1. Study design

This study used baseline data from 1001 children within the Child Health Agricultural Pesticide Cohort Study in South Africa (CapSA) (Chetty-Mhlanga et al., 2018). The research was conducted in three areas with distinct agriculture production in the Western Cape between 2017 and 2019. The areas include the Hex River Valley (mainly table grapes), Grabouw (mainly stone fruits) and Piketberg (mainly cereals). Children aged nine to 16 years old were recruited from seven schools attending grades two to nine. To ensure a pesticide exposure contrast in terms of proximity to agriculture fields, children were purposely enrolled from farms and villages. Children were interviewed at baseline in 2017 on the school premises using the smartphone-based application Open Data Kit (ODK) to enquire about their exposures and headache symptoms. Thereafter participants were assessed on cognitive functioning, individually for a 40 -minute period via a neurocognitive software assessment tool on tablets. In addition an interview was conducted between 2018 and 2019 with the guardians (n = 482) of the children at their home. The interview covered questions on socio-demographics including education, employment, language, household size.

2.2. Health outcomes

2.2.1. Two standardized health outcome tools were used for the assessment of health outcomes including

2.2.1.1. Headache scores. The headache Impact Test (HIT-6) was included in the participant survey, with six questions on the severity of headaches using a five-point Likert scale for responses ranging from never to always and resulting in a score ranging from 36 to 78 (Kosinski et al., 2003).

2.2.1.2. Neurocognitive assessment. A neurocognitive assessment battery, the Cambridge Automated NeuroPsychological Battery (CANTAB) of six tests across three cognitive domains (memory, attention and processing speed) was conducted (see study protocol paper for descriptive details). (Chetty-Mhlanga et al., 2018). The six CANTAB tests recorded several performance scores, including latency and accuracy for each task within each test: Motor Screening (MS); Reaction Response (RR); Spatial Working Memory (SWM); Paired Associate Learning (PAL); Multi-tasking (MTT); Rapid Visual Information Processing (RVP) (see Supplementary for test description, Table S1) (Chetty-Mhlanga et al., 2018). The latency scores in milliseconds per task were inverted to a speed measure to obtain a near normal distribution of the data. For consistent result presentation inaccuracy scores were converted to accuracy scores by subtracting the inaccuracy score from the maximum achievable score. Outliers were excluded if any value was 3.25 standard deviations above and below the mean.

2.3. Pesticide exposure assessment

We explored the pesticide exposure from the participant surveys by asking about different farm and leisure activities that result in ingestion of potentially contaminated water or food, inhalation of gases in air or dust or direct dermal contact with the body.

Specifically the following aspects were inquired in the interview: 1) child farm activities related to pesticide handling; 2) eating crops directly from the field; 3) contact with surface water around the field; and 4) seen and smelt pesticide spraying activities. Involvement in farm activities was defined to have done any of these activities: helped with picking fruits in the field/vineyard/orchard; helped with cleaning farm equipment; assisted in pesticide storage; helped with burning any pesticide or chemical containers and helped with pesticide or chemical spraying, mixing or loading.

To account for any difference between potential acute and long-term exposure, participants were asked about long-term exposure and short-term exposure by enquiring about “ever” exposure as well as exposure “in the last 7 days”.

2.4. Statistical analysis

We conducted linear regression models to calculate associations between pesticide exposure proxies and headache and nine cognitive test scores. Models were a priori adjusted for demographic and lifestyle variables of area, age, grade, sex, head injury (severe head accident or potential Traumatic Brain Injury), smoking, alcohol and drugs. In-depth analysis gave indication of confounding for two lifestyle exposure variables relevant to this cohort: mobile phone ownership and problematic mobile phone use (Chetty-Mhlanga et al., 2020).

For a subset of the cohort (n = 482), additional sociodemographic variables were available from the guardian survey (Chetty-Mhlanga et al., 2018). Thus, an additional analysis was conducted with this subgroup, where models were additionally adjusted for five socio-demographic variables (home language, maternal education, maternal employment, government grant, household size). Further, a sensitivity analysis was conducted with the full cohort on gender and age stratification. All regression models were stratified by two age groups, children (9.0–11.9 years) and adolescents (12.0–16.1).

There was a substantial overlap between the group of recent (“In the past 7 days, how often did you…”) and long-term (“have you ever…”) exposure proxies (Supplementary Fig. 1). For this reason, we only conducted analyses related to ever exposure but not to recent exposure.

In order to evaluate dose-related associations, a separate analysis was done for eating crops from the field/vineyard/orchard in relation to washing behavior and picking crops in relation to wearing Personal Protective Equipment (PPE). For the combination of the exposure variable, “eating crops” and “washing fruits” low exposure (0) corresponds to “never eat fruit” and “always wash fruit”, moderate exposure (1) corresponds to “eat crops from the field and sometimes or always washing fruit”, and high exposure (2) corresponds to “eat fruit and never or rarely washing fruit”. For the combination of the exposure variable “picking crops” and “use of PPE”, low exposure (0) corresponds to “never pick crops”, moderate exposure (1) corresponds to “pick crops with PPE” and high exposure (2) corresponds to “pick crops without PPE”.

3. Results

Table 1 shows the characteristics of the study population, see Supplementary Table S2, stratified by gender and study area. The 1001 school-children aged nine to 16 years (mean: 11; SD: ±1.7) from grades two to nine (5; ±1.5) were distributed almost equally over three study areas and across gender (Table S2). Guardian interviews were conducted with 482 participants. One third (32%) use a mobile phone for calls, texting or the internet and 46% engage in screen time (e-media device and the internet). Previous head injury was reported by 34%, while 15% are smoking, 16% drink alcohol and 2% consume other drugs.

Table1
Demographics of the children at baseline enrolled in the cohort study in the Western Cape, South Africa between 2017 and 2019, separate for the whole cohort and the sub cohort with guardian interviews.

**TBI –Traumatic Brain Injury*	**Total n (%)**	**Sub-cohort Total n (%)**
TOTAL n (%)	**1001(100)**	**482 (100)**
Age categories		
9–11 years	592 (59.1)	284 (59)
12–14 years	356 (35.6)	164 (34)
15–16 years	53 (5.3)	34 (7)
Grade categories		
2nd-3rd	163 (16.3)	79 (16)
4th-6th	667 (66.6)	310 (64)
7th-9th	171 (17.1)	93 (20)
Head Injury (ever)		
0 (none)	659 (65.9)	304 (63)
1 (fell & hit head)	230 (23.0)	116 (24)
2 (potential TBI*)	112 (11.2)	62 (13)
Smoke (ever)		
No	854 (85.4)	410 (85)
Yes	147 (14.7)	72 (15)
Alcohol Use (ever)		
No	851 (85.1)	395 (82)
Yes	150 (15.0)	87 (18)
Drug Use (ever)		
No	976 (97.6)	468 (97)
Yes	25 (2.5)	14 (3)
Indoor leisure activities		
Mobile Phone Use (current)		
No	683 (68.3)	350 (73)
Yes	318 (31.8)	132 (27)
Electronic Media Use (current)		
No	540 (54.0)	284 (59)
Yes	461 (46.1)	198 (41)

Regarding pesticide exposure (Supplementary Table S3), around 46% of the children live on farms, with the highest proportion (62%) living on farms in the Grabouw area. In total, 47% and 66% of the participants have parents or family members who work on a farm respectively. Pesticide spraying was reported by 80% of the study participants, with the highest in the Grabouw area, predominantly via tractor spraying while 52% reported smelling pesticide spraying. About 50% of the cohort participated in all three farm and leisure activities with significant differences between study areas and gender (Supplementary Table S4).

Figs. 1 and 2 illustrate the pesticide exposure proxies across the three study areas. In total, 24.6% engaged in pesticide-related farm activities, 51.5% are eating crops from the field and 49.4% are swimming in surface water. Picking fruit, cleaning and storing pesticide equipment are the most frequently reported farm activities (47.4%) and are most prevalent in De Doorns. De Doorns was also the area where most children reported engaging in leisure activities, with almost 70% eating crops directly off the field/vineyard/orchard, and over 50% playing, swimming or bathing in nearby water in both De Doorns and Grabouw. Moderate overlap was observed between different exposure proxies as shown in Supplementary Fig. S2.

Table 2 shows the association between change in headache and six cognitive performance outcome scores in relation to farm activities, eating crops and leisure-related activities. The headache impact test score was consistently increased in relation to all three pesticide exposure proxies. Most of the cognitive tests showed a negative association with pesticide exposure although only three associations reached statistical significance; motor screening speed and accuracy of rapid visual information processing in relation to eating crops directly from the

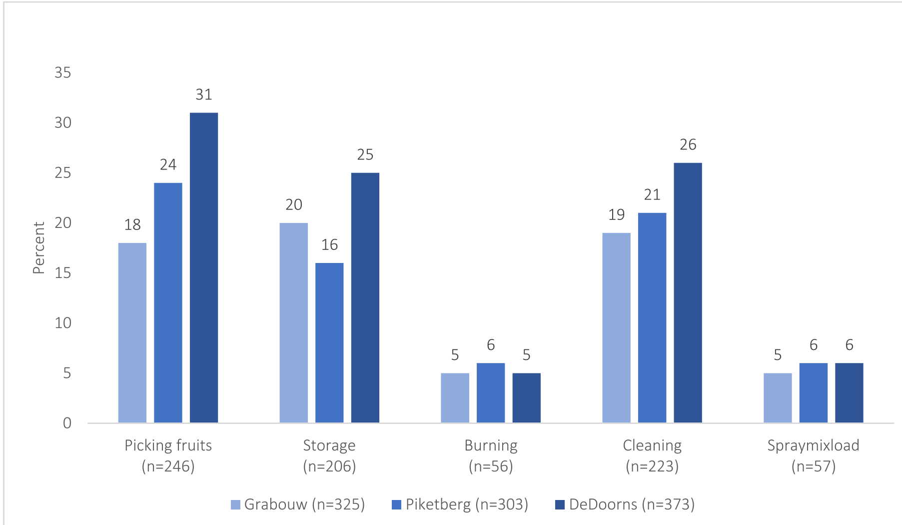

Fig. 1. The individual pesticide-related farm activities which children ever performed stratified across the three agricultural farm areas.

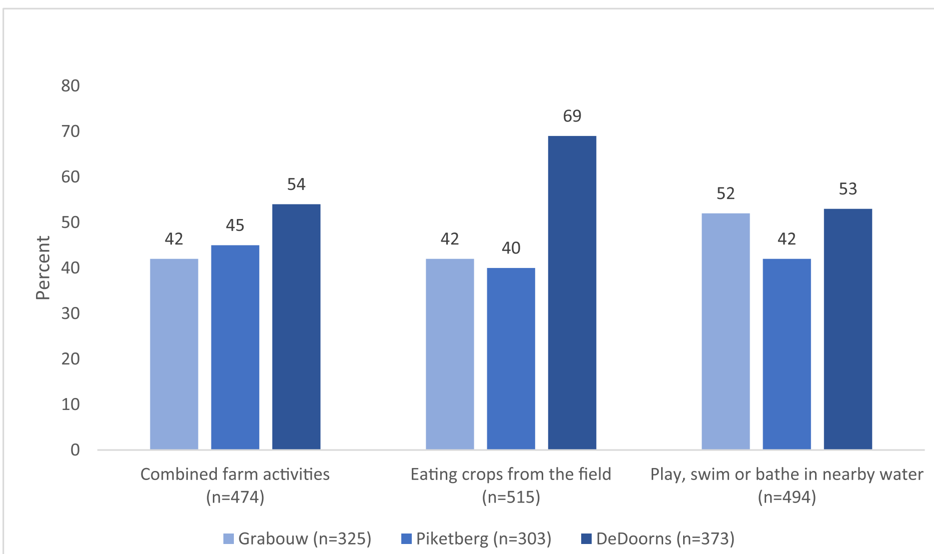

Fig. 2. Pesticide-related farm and leisure time activities which children ever performed stratified across the three agricultural farm areas.

Table 2
Linear regression analysis results from the full sample: associations of three pesticide-related exposures with headache score and six cognitive performance outcome scores. Beta refers to a difference in scores between exposed and unexposed study participants.

			Farm activities (n = 474)			Eating (n = 515)			Leisure (n = 494)		
	Score	N	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Symptom											
Headaches	Total	999	**1.99**	**0.86; 3.12**	**<0.01**	**1.52**	**0.41; 2.67**	**<0.01**	**1.25**	**0.18; 2.33**	**0.02**
Processing Speed											
Motor Screening	Speed (seconds)	997	0.04	−0.01; 0.10	0.12	**−0.06**	**−0.11; 0.01**	**0.02**	0.00	−0.05; 0.05	1.00
Reaction Response	Speed	961	−0.10	0.24; 0.05	0.18	−0.13	−0.28; 0.01	0.07	−0.07	−0.20; 0.07	0.34
Attention											
Rapid Visual Processing	Speed	981	−0.04	−0.14; 0.06	0.43	−0.02	−0.12; 0.08	0.70	−0.05	−0.14; 0.05	0.33
	Accuracy (hits)	984	0.00	−0.10; 0.01	0.51	**−0.02**	**−0.03; 0.00**	**0.02**	0.00	−0.13; 0.01	0.93
Multi-tasking	Speed	986	0.01	−0.02; 0.04	0.43	0.00	−0.03; 0.02	0.84	−0.02	−0.04; 0.01	0.27
	Accuracy	994	**−2.74**	**−5.19; −0.29**	**0.03**	0.04	−2.43; 2.51	0.98	−1.69	−4.09; 0.71	0.17
Memory											
Paired Associates Learning	Accuracy	969	−0.44	−0.96; 0.08	0.10	−0.45	−0.96; 0.06	0.08	−0.24	−0.73; 0.26	0.35
Spatial Working Memory	Accuracy	991	−0.03	−0.76; 0.69	0.93	−0.40	−1.11; 0.31	0.27	−0.08	−0.78; 0.61	0.81
	Strategy	991	−0.06	−0.25; 0.14	0.56	0.00	−0.19; 0.19	0.96	−0.17	−0.35; 0.01	0.07

*Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership.

field/vineyard/orchard, as well as accuracy of a multitasking test in relation to farm activities.

Model coefficients in the subgroup with additional socio-demographic information (Table 3) were somewhat different from those in the full sample (Table 2), also with wider confidence intervals due to the smaller sample size. However, coefficients did not noticeable vary between the two adjusted models in the same subgroup sample (Table 3) indicating that confounding by socio-demographic factors did not explain these differences.

Analysis of headache and cognitive performance scores in relation to eating crops from the field combined with washing fruit did not indicate hypothesized consistent exposure–response pattern between these exposure proxies and the outcomes (Supplementary Table S5). The headache severity score was significantly lower in the high-exposure group. For cognitive tests, reduced reaction response speed was observed in the moderate-exposure group and increased rapid visual information processing speed in the high exposure group. Further, lower accuracy in a multi-tasking test was observed in the high-exposure group.

Table 4 presents results on the association in headache and cognitive performance scores in relation to picking crops with PPE. The headache score was significantly higher in both, the moderate and the high-exposure groups compared to the reference group. For cognitive functions, two significant negative associations were observed for the moderate-exposure group, with a lower memory accuracy and memory strategy score compared to those who do not pick crops but no significant associations in the high exposure group. Additional adjustment for sociodemographic factors (Table 5) had little impact on the headache and the cognitive testing scores.

Overall, no specific pattern of association is found between the individual farm activities and neurocognitive health outcome scores (see Supplementary Table S7). The headache score is significantly increased for those who store pesticides but not amongst the other farm exposure activities.

Fig. 3 displays the association between differences in headache scores in relation to having seen pesticide spraying in nearby fields and having smelled pesticide after spraying. A significant exposure-repose relationship is observed for the headache score in relation to reported frequency of these environmental exposures. No association is observed between these two environmental exposure proxies and neurocognitive performance. Age stratified analysis did not reveal systematic different association patterns between the 9 to 11 year old and the 12 to 16 year old study participants (Tables S9 and S10). No consistent differences were observed between female and male study participants.

4. Discussion

After using various pesticide related activities and behaviors as a surrogate measure for long-term pesticide exposure, our results suggest an overall negative effect of long-term pesticide exposure on headache and cognitive functioning, although mostly non-significant for the latter.

Characterizing exposure to a broad mixture of pesticides is complex within agricultural communities due to the unknown and unpredictable exposure pathways related to activity patterns of exposed persons, the variety of pesticides used and the intensity at which people are exposed through their environment (Fenske et al., 2000). Previous studies have found high pesticide exposure in farmworkers children due to take-home pesticide exposure (Hyland and Laribi, 2017). A recent study found that urine metabolites were higher in school children who ate fruit at school (Muñoz-Quezada et al., 2019). This corresponds with significant differences in the association of higher pesticide metabolites amongst farmworkers and their families eating vegetables during the harvest season, compared to the vegetable consumption of non-farmworkers (Holme et al., 2016). Similarly, increased biomarkers amongst pre-schoolers living in agricultural areas, is suggestive of increased dietary intake and mobility/activity (Li et al., 2019). These studies support our most consistent association with eating crops from the vineyard or orchard on cognitive functioning. A thesis on vulnerable populations in The Gambia, reveals that the risky practices of agricultural children were reported to include: “not wearing PPE; mixing and applying with bear hands; storing pesticides in the home; inadequately disposing of pesticide containers and wearing shoes in the home after working with pesticides” (Butler-Dawson et al., 2016). This also demonstrates that pesticide exposure is correlated with various behaviors and activities (Li et al., 2019). In our study we thus used characteristics and activities related to pesticides exposure. Many other studies of postnatal exposure focus on metabolites to determine previous exposure. Such biomarkers are doubtless information for exposure

Table 3
Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in headache score and 6 cognitive performance outcome scores in relation to three pesticide related exposures between those who engage in these activities and those who do not.

	Score	n	Farm activities (n = 225)		Eating (n = 273)		Leisure (n = 230)	
			Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*	Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*	Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*
Symptom								
Headaches	Total	481	1.04 (−0.60; 2.69)	1.21 (−0.46; 2.89)	1.59 (−0.01; 3.21)	1.59 (−0.06; 3.25)	1.07 (−0.53; 2.67)	1.05 (−0.57; 2.66)
Processing Speed								
Motor Screening	Speed (seconds)	482	**0.10 (0.02; 0.18)**	**0.09 (0.01; 0.17)**	−0.03 (−0.11; 0.04)	−0.01 (−0.09; 0.07)	−0.02 (−0.10; 0.05)	−0.02 (−0.09; 0.06)
Reaction Response	Speed	458	−0.17 (−0.38; 0.04)	−0.19 (−0.40; 0.02)	−0.19 (−0.39; 0.02)	−0.20 (−0.40; 0.01)	−0.11 (−0.31; 0.09)	−0.10 (−0.31; 0.10)
Attention								
Rapid Visual Info Processing	Speed	472	0.05 (−0.09; 0.19)	0.07 (−0.07; 0.22)	0.03 (−0.11; 0.17)	0.03 (−0.11; 0.17)	−0.01 (−0.15; 0.13)	0.00 (−0.14; 0.13)
Multi-tasking	Speed	474	0.00 (−0.04; 0.04)	0.00 (−0.04; 0.04)	0.00 (−0.04; 0.04)	0.00 (−0.03; 0.04)	−0.03 (−0.07; 0.01)	−0.03 (−0.07; 0.01)
Memory								
Paired Associates Learning	Accuracy (hits)	462	0.09 (−0.68; 0.86)	0.04 (−0.75; 0.83)	−0.64 (−1.40; 0.12)	−0.63 (−1.41; 0.14)	−0.22 (−0.98; 0.52)	−0.17 (−0.93; 0.59)
Spatial Working Memory	Strategy	477	−0.02 (−0.30; 0.26)	−0.01 (−0.29; 0.27)	−0.01 (−0.28; 0.26)	0.03 (−0.25; 0.31)	−0.05 (−0.32; 0.22)	−0.05 (−0.32; 0.21)

Adjusted = sex, age, grade, area, head injury, smoke, alcohol, drugs, farm residence, farm residence, mobile phone ownership, problematic mobile phone use.
*Adjusted+ = Adjusted + mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support.
Data presented as the Beta from linear regression models.

Table 4
Linear regression analysis results from the full sample: changes in the headache score and six cognitive performance outcome scores in relation to picking fruits combined with wearing protective equipment.

	Picking and Protective wear							
	Ref (n = 755)		Moderate Exposure (n = 141)			High Exposure (n = 105)		
		n	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Health Symptom.								
Headaches	Total	999	**2.57**	**1.02;4.11**	**<0.01**	**1.92**	**0.18; 3.65**	**0.03**
Processing Speed								
Motor Screening	Speed	997	0.04	−0.04;0.11	0.30	−0.04	−0.12; 0.05	0.41
Reaction Response	speed	961	0.02	−0.17;0.22	0.80	−0.18	−0.40; 0.04	0.11
Attention								
Rapid Visual Info Processing	Speed	981	−0.12	−0.26; 0.01	0.08	0.01	−0.14; 0.16	0.86
	accuracy	984	0.00	−0.02; 0.02	0.81	−0.02	−0.04; 0.01	0.16
Multi-tasking	Speed	986	0.02	−0.02;0.06	0.33	−0.01	−0.05; 0.03	0.73
	accuracy	994	−1.03	−4.48; 2.42	0.56	−2.99	−6.85; 0.88	0.13
Memory								
Paired Associates Learning	accuracy	968	**−0.88**	**−1.60; −0.17**	**0.02**	−0.30	−1.10; 0.50	0.46
Spatial Working Memory	accuracy	990	0.32	−0.67; 1.32	0.52	−0.40	−1.52; 0.71	0.48
	strategy	990	**−0.29**	**−0.56; −0.03**	**0.03**	0.10	−0.20; 0.39	0.51

*Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership.
Ref = low exposure "never pick crops", moderate exposure= "pick crops with PPE", high exposure ="pick crops without PPE".

Table 5
Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in the headache score and six cognitive performance outcome scores in relation to picking fruits combined with wearing protective equipment.

	Picking and Protective wear					
	Ref (n = 366)		Moderate Exposure (n = 68)		High Exposure (n = 48)	
		n	Beta (β) 95% CI Adjusted	Beta (β) 95% CI Adjusted+*	Beta (β) 95% CI Adjusted	Beta (β)95% CI Adjusted+*
Health Symptom.						
Headaches	Total	481	**3.04**	**3.37**	0.98	1.19
			0.75; 5.34	**1.01; 5.72**	−1.58; 3.54	−1.40; 3.79
Processing Speed						
Motor Screening	Speed	482	0.03	0.05	0.00	0.01
			−0.08;0.14	−0.07; 0.16	−0.12; 0.12	−0.11; 0.13
Reaction Response	speed	458	−0.02	−0.02	−0.07	−0.06
			−0.31; 0.23	−0.32; 0.28	−0.39; 0.25	−0.39; 0.26
Attention						
Rapid Visual Info Processing	Speed	472	−0.01	−0.01	−0.16	−0.16
			−0.21; 0.19	−0.21; 0.20	−0.38; 0.06	−0.38; 0.06
	accuracy	473	−0.00	−0.00	−0.02	−0.02
			−0.03; 0.03	−0.03; 0.03	−0.06; 0.01	−0.06; 0.01
Multi-tasking	Speed	474	0.02	0.02	−0.03	−0.02
			−0.03;0.07	−0.03;0.08	−0.09; 0.04	−0.08; 0.04
	accuracy	477	−1.86	−1.68	−4.05	−4.07
			−7.03; 3.33	−7.00; 3.63	−9.81; 1.73	−9.91; 1.78
Memory						
Paired Associates Learning	accuracy	462	−0.73	−0.78	−0.32	−0.38
			−1.83; 0.38	−1.91; 0.35	−1.54; 0.92	−1.62; 0.87
Spatial Working Memory	accuracy	476	0.31	0.36	−0.76	−0.73
			−1.17; 1.78	−1.15; 1.88	−2.41; 0.88	−2.39; 0.94
	strategy	477	−0.26	−0.24	−0.16	−0.16
			−0.65; 0.13	−0.63; 0.15	−0.27; 0.59	−0.27; 0.60

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership.
*Adjusted+ = Adjusted + mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support.
Data presented as the Beta from linear regression models.
Ref = low exposure "never pick crops"), moderate exposure ="pick crops with PPE", high exposure ="pick crops without PPE".

assessment. However, there is uncertainty to what extent such measures reflect long term exposure as biological half life time is short for the majority of metabolites. Thus, our activity related exposure surrogates may represent a more stable measure for long term pesticide exposure. We asked about recent and long-term pesticide exposure related activities and found very high agreement, indicating that such activities represent a long-term behavior. However, we could not validate, to what extent hypothetical exposure proxies correspond with actual exposure. For instance, we expected that children reporting washing fruit and wearing PPE during crop picking may have low pesticide exposure. However, we could not find consistent exposure–response patterns in relation to these protective measures. A possible explanation might be reverse causality that applying protective measures is correlated with higher likelihood of pesticide contact, in general. Thus, overall exposure for children taking protection measures may not be as low as anticipated. In addition, we cannot account for bias in self-reports and the quality (re-used or new) and compliant use of PPE provided to the children from the type of exposure data we have used in this analysis.

Another challenge for interpretation is the fact that the same behavior may result in exposure to different types of pesticides,

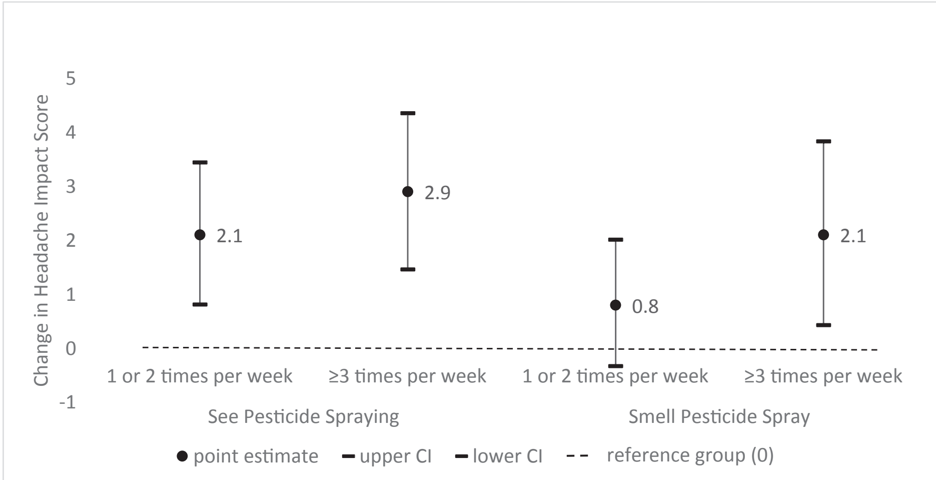

Fig. 3. Change in headache impact score in the full sample relation to the gradient of exposure to seeing and smelling pesticide spray.

depending on the area, the type of agriculture or the season. Various pesticides may have different neurocognitive effects, which may explain why we could not identify, except for headache, consistent exposure–response associations for any of the cognitive tests. The complex mixtures of pesticide exposure situation has been demonstrated in a recent measurement study in rivers of our three study areas (Curchod et al., 2020). A total of 53 pesticides were above the limit of detection, some of them in high concentrations. The majority of OPs include the neurotoxic ingredients atrazine, diazinon, chlorpyrifos and malathion, two of which, carbaryl and imidacloprid, are banned in the EU. Similar results were found in an analysis of 27 current-use pesticides in air at 20 sampling sites across Africa with six sites from the Western Cape (Fuhrimann et al., 2020).

4.1. Strength and limitations

A strength of this study is the cognitive outcome assessment using standardized tests administered on a Tablet, which is in line with suggestions of clinicians to measure the neurotoxic effects of children, specifically in three domains: memory, executive functioning and attention (Vorhees et al., 2018; Carrillo et al., 2016). This approach is unlikely to create a bias with respect to the exposure assessment. Limitations of the study include the cross-sectional design, limiting conclusions regarding causal inference of observed associations. The sample size of certain farm activities are relatively small and thus the power of the study is limited, which may be an explanation for the many non-significant results despite an overall indication of negative exposure impact. The study includes self-reported exposure measures and we have not validated how well these measures correspond to objective measures such as metabolites in urine or in hair samples. The latter have been found to be reliable measure of long-term exposure to pesticides amongst child workers employed in farming, and were suggested for an ongoing monitoring program for genotoxicity and consequent biological health effects (Vidi et al., 2017). The complexity of pesticide mixtures detected in the air and water sampling, and the different types of pesticides, depending on the area, the type of agriculture or the season will be considered in the next steps of the analysis with objective data to link these behaviors to specific pesticide groups. As in every observational study, confounding may also be of concern. For a subset of the cohort, we additionally adjusted for five socio-demographic variables derived from the guardian survey. However, this had little effect on the regression coefficients (Table 3, Table 5 and Table S8), indicating that residual confounding is unlikely to play a major role in this analysis.

4.2. Implications

Literature on long-term pesticide exposure in school-aged children is still rare. A study examining the long-term cognitive effects in cumulative exposure between adolescent applicators and non-applicators, over three seasonal time-points, concluded that the deficits in neurobehavioral performance was consistently observed amongst the high exposure group compared to the low exposure groups, even months after the application season (Rohlman et al., 2016). The specific cognitive deficits in executive functioning, memory and behavioral attention in this study (Rohlman et al., 2016), coincides with our findings, as well as three systematic reviews on the association of pesticides to neurodevelopment (González-Alzaga et al., 2014; Ross et al., 2012; Ntzani et al., 2013), including the effects in 6–9 year olds living in the vicinity of banana plantations, exposed to chlorpyrofis, mancozeb and pyrethroids (van Wendel de Joode et al., 2016). A study using the same CANTAB tool in OP self-poisoned patients coincides with impairment in the same sub-domains of attention (rapid visual processing) and memory (paired associates learning and spatial working memory strategy) as our study participants who engage with eating and picking crops directly from the field (Dassanayake et al., 2020). In a study of mice, long-term low-dose exposure to malathion (an insecticide) was found to cause cognitive and spatial working memory impairment (dos Santos et al., 2016; van Wendel de Joode et al., 2016). A recent review concluded that low-level pesticide exposure of children may increase the risk to develop Attention Deficit Hyperactivity Disorder (ADHD) and autism (Roberts et al., 2019).

Based on our results and recent studies on pesticides and their burden of cardiovascular disease and respiratory health (Darçin and Darçin, 2017), a stricter control on management, storage, packaging and several processes after sales of pesticide is warranted. Given that these participants are not in occupation, a recommendation is to implement an educational program on pesticide related activities in schools and to learn from current interventions and their effectiveness (Griffith et al., 2019 May; Muñoz-Quezada et al., 2019; Rohlman et al., 2020 Dec). Given South Africa's history and socio-economic divide to the farm laborers with short-term working contracts, future interventions should aim to reduce the health risks of these vulnerable populations including their children.

5. Conclusion

Our results are suggestive of long-term detrimental health effects on headaches and cognitive function amongst children in these agricultural communities engaged in pesticide-related farm and leisure activities, specifically eating crops off the field and picking crops from the field. Our findings are novel since this is one of the few studies to address specific activities associated with pesticide exposure in this specific age group. As a next step, longitudinal analysis with biomarkers are needed to validate these pesticide exposure proxies.

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Ethical approval

The ethical protocols for the study on pesticide exposure and reproductive health outcomes has been approved by the University of Cape Town's Human Research Ethics Committee (HREC reference number: 234/2009). An amendment was made to this protocol for the addition of neurobehavioral outcome and submitted for ethical clearance, which was approved on 24 May 2017 by the University of Cape Town's Human Research Ethics Committee (reference: 234/2009). The Swiss Tropical Pubic Health Institute Research Commission has ethically approved the proposal for the neurobehavior study in April 2017 (reference: EKNS 2017-01683). In addition, the Western Cape Education Department has provided approval and consent to conduct this study amongst the children who attend school in these study areas (reference: 20150629-846).

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106237.

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