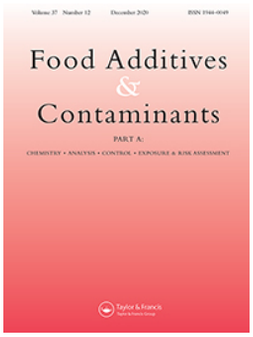

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Nutrition and growth outcomes are affected by aflatoxin exposures in Kenyan children

Ruth Nabwire Wangia-Dixon[a], Kathy Siyu Xue[a], Jessica Alcala[a], Trang Ho Thu Quach[b], Xiao Song[b], Lili Tang[a], James Ombaka[c], David Peter Githanga[d,e], Omu Aggrey Anzala[e,f], and Jia-Sheng Wang[a]

[a]Department of Environmental Health Science, University of Georgia, Athens, Georgia, USA; [b]Department of Epidemiology and Biostatistics, University of Georgia, Athens, Georgia, USA; [c]School of Public Health and Community Development, Maseno University, Maseno, Kenya; [d]Peadiatrics, Cardiology and Child Health, Nairobi Hospital, Nairobi, Kenya; [e]Medical Microbiology Department, University of Nairobi, Nairobi, Kenya; [f]KAVI Institute of Clinical Research, University of Nairobi, Nairobi, Kenya

ABSTRACT

Aflatoxin exposure, malnutrition and growth impairment in children present significant public health problems in low- and middle-income countries. Recent epidemiology studies show that exposure to aflatoxins through dietary sources in early life contributes to growth retardation among children. However, the findings remain inconclusive due to limited comparative studies in high versus low aflatoxin exposure regions. This cross-sectional study presents aflatoxin exposure levels among children aged 6 to 12 years, and further evaluates the association between aflatoxin exposure levels, malnutrition and growth impairment in Kenya, East Africa. AFB_1-lysine adducts are validated biomarkers of exposure and were quantified using HPLC with fluorescence detection. All children (n = 746) had detectable levels of AFB_1-lysine adducts in serum, range 0.65–518.9 pg/mg albumin with a geometric mean (GM) of 10.5 (95%CI 9.4–11.7) pg/mg albumin. The Geometric Means (GM) of AFB_1-lysine adducts were 14.0 (95%CI 12.5, 15.7) pg/mg albumin and 8.2 (95%CI 7.6, 8.8) pg/mg albumin (p-value < 0.001), among children recruited from Makueni and Siaya Counties, respectively. While the study confirms higher human exposure levels in Makueni county, it provides an initial data set for aflatoxin exposure levels among children recruited from Siaya County. In multivariate analysis, after adjusting for socio-economic indicators, farming practices, and household dietary patterns, increasing one unit of log AFB_1-lysine was associated with decreasing Weight-for-age z-score (WAZ) by −0.13, p-value = 0.019 among all children aged 6–12 years. Among children 6 to 9 years, WAZ decreases by −0.11 (−0.54, −0.01), p-value = 0.049. Additional growth parameters Height-for-age z-score (HAZ) and Weight-for-height z-score (WHZ) do not reach statistical significance. HAZ decreases by −0.08, p-value = 0.337 and WHZ decreases by −0.17, p-value = 0.437 with every increase in log AFB_1-lysine. These data suggest that efforts must be put in place to control for aflatoxin exposure in order to achieve better growth outcomes.

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Children; aflatoxins; AFB_1-lysine; malnutrition; stunting; underweight; wasting

Introduction

Aflatoxins (AFs), are naturally occurring secondary metabolites of *Aspergillus flavus, Aspergillus parasiticus* and other *Aspergilla* strains (IARC 2002; CAST 2003). AFs were originally discovered in the 1960s after the outbreak of the Turkey X disease in England which contributed to deaths of more than 100,000 turkey poults fed meals containing peanuts imported from Brazil (Lancaster et al. 1961; Sargeant et al. 1961). To date, up to 16 structurally related AFs have been identified and characterised, among which aflatoxin B_1 (AFB_1) is the most potent (Asao et al. 1963; Spensley 1963; Kensler et al. 2011). AFs contaminate a variety of food crops including cereals, legumes, oilseeds, nuts, milk, meat products, spices, coffee and tea (IARC 2002; CAST 2003). Globally, an estimated 25% of food crops are contaminated by AFs and other mycotoxins (Daniel et al. 2011; Sarma et al. 2017). The maximum limit of AFs in food for human consumption varies for different countries but the range is 2–20 μg/kg for various foods (USFDA 2000; European Commission 2006; Wu et al. 2012). Total AFs contamination levels exceeded the recommended limits of 10 μg/kg in cereals collected from current study population (Nabwire et al. 2020). Moreover, the African continent has been reported to suffer economic losses of up to 670 million USD annually in earned revenue due

CONTACT Jia-Sheng Wang jswang@uga.edu Department of Environmental Health Science, University of Georgia, Athens, Georgia 30602, USA

to rejection of AFs-contaminated foods. On the contrary, the United States spends an estimated 500 million USD in controlling AFs in peanuts, corn and other crops (IARC 2015; Wu 2015; JECFA 2018).

Worldwide, up to 4.5 billion people are unintentionally exposed to AFs through dietary sources. AFs exposure can occur *in utero*, via breast milk, through weaning foods and throughout an individual's lifetime (Shuaib et al. 2012; Groopman et al. 2014). Other routes of exposure through inhalation and dermal penetration occur in occupational settings and have been reviewed (Wangia et al. 2019b). Short-term exposure to AFs in cereal-based foods for human consumption has been identified to result in aflatoxin poisoning clinically identified as aflatoxicosis (Kamala et al. 2018; Narsimha Reddy and Raghu Raghavender 2007; Ngindu et al. 1982; Probst et al. 2007). Clinical manifestations of aflatoxicosis in human populations include haemorrhage, jaundice, liver cirrhosis, liver failure and ultimately death. The case fatality rate of aflatoxicosis reported in human populations ranges from 39 to 50% (Ngindu et al. 1982; Kamala et al. 2018). Human deaths from aflatoxicosis have been reported in India, Kenya and Tanzania (Kamala et al. 2018; Narsimha Reddy and Raghu Raghavender 2007; Probst et al. 2007). Recurring aflatoxicosis outbreaks have been reported in Kenya since 1981 (Ngindu et al. 1982). Between 2004 and 2014, the Kenya ministry of Health estimated that subsequent outbreaks have affected nearly 600 individuals and resulted in over 211 deaths (Awuor et al. 2017; Wangia 2017). Additionally, incidences of acute aflatoxicosis in animals have been reported worldwide with the severity of poisoning dependent on species, age, sex and nutritional status of the exposed subjects. In animals, AFs poisoning was associated with gastrointestinal dysfunction, reduced feed utilisation, anaemia, jaundice and in most cases, hepatic necrosis (Hintz et al. 1967; Di Gregorio et al. 2017; Sarma et al. 2017). Additionally, relatively high aflatoxin exposure in the range 0.5 to 1.0 mg/kg is associated with decreases in iron absorption, low haematocrit counts and microcytic hypochromic anaemia in dogs, rabbits, catfish and poultry and have been thoroughly reviewed (Smith et al. 2017). Jointly, studies on negative impacts of aflatoxin contamination have been elemental in making a case for regulation and control of widespread exposures.

The cumulative effects of exposure in the long term are more pronounced. AFB_1 is an established Group I human carcinogen linked to primary liver cancers (IARC 1993, 2002). It is well-known that more than 50% of primary liver cancer cases in South East Asia are attributed to consumption of AFs-contaminated food products, which is further compounded by Hepatitis B virus infections (Liu and Wu 2010; Palliyaguru and Wu 2013; Magnussen and Parsi 2013). AFs are also immune toxicants and rapid progression of infectious diseases such as HIV to AIDs has been reported in Ghana and Uganda among individuals with high AFs metabolites in their sera (Jolly et al. 2011; Kang et al. 2015). The role of AFs in immune-modulation is attributed to immune suppression and impaired liver function.

Numerous studies evaluating the role of AFs exposure in early life through dietary sources such as breast milk and weaning foods postulated that chronic exposures may be a major contributing factor to malnutrition and impaired growth in children (IARC 2015). The classical use of anthropometric parameters as a proxy for malnutrition in children is widely accepted due to the non-invasive nature of data collection. Conventionally, a child's weight and height are used to calculate weight-for-age-z-score (WAZ), height-for-age Z-score (HAZ) and Weight for Height Z-score (WHZ), which are standardised per the World Health Organisations recommendations (WHO 1986; de Onis and Onyango 2008). All children with WAZ, HAZ and WHZ scores less than −2 are generally categorised as Underweight, Stunted and Wasted, respectively. Numerous studies have reported on the association between aflatoxin exposures and stunting (HAZ <-2) (Kimanya et al. 2010, Magoha et al. 2016, Gong et al. 2004; Turner et al. 2007). Nonetheless, a critical assessment reveals that stunting is fraught with issues since children who are stunted are normally a subset of children with various growth impairments. For example, growth retardation implies that groups of children are too short for their age but does not imply they are stunted (Leroy and Frongillo 2019). Therefore, in addition to using height-for-age, weight-for-age and weight-for-

height z-scores as continuous variables, we assess the effect of aflatoxin exposures against additional growth parameters namely, body mass index (BMI) and mid-upper-arm circumferences (MUAC) because both are effective in assessing morbidity and mortality risks associated with undernutrition among African school-aged-children (Mramba et al. 2017). Moreover, the dangers of AFs exposure to public health are greater than earlier suspected since underweight, stunted and/or wasted children are significantly at higher risk of dying from infectious diseases, increased health problems, cognitive impairments, lower school achievements, reduced life-time earnings, and decreased productivity (Black et al. 2008; Ahlberg et al. 2018).

While recent epidemiology studies have reported that exposure to AFs through dietary sources in early life contributes to growth retardation among children, the findings are inconsistent and remain inconclusive (Shirima et al. 2015; Mitchell et al. 2017; Watson et al. 2018). Longitudinal studies such as one conducted in Benin reported an inverse association between aflatoxin exposure and HAZ (Gong et al. 2004); a different study by Turner et al. reported an inverse association with both HAZ and WAZ in the Gambia; while Kimanya et al. and Magoha et al. reported small but significant inverse association between aflatoxin exposure and both WAZ and HAZ (Kimanya et al. 2010, Magoha et al. 2016). Additional longitudinal studies in Bangladesh, Southern Mexico and Tanzania that enrolled children below 3 years old reported no association between aflatoxin exposure and growth parameters (Mahfuz et. al 2019, Leroy et al. 2018, Chen et al. 2018; Magoha et al. 2016; Shirima et al. 2015). These studies however either do not properly control for confounders and/or were done in high altitude regions with cooler temperatures and thus, the effects of early exposures cannot be easily elucidated. Furthermore, a Nigerian study reported that children of less than 4 years with AFB_1-lysine exceeding 4.5 pg/mg were more likely to be wasted (WHZ < −2) and/or stunted (HAZ < −2) (McMillan et al. 2018). Additionally, the prevalence of stunting and/or underweight associated with AFs exposure were reported to be 33 and 29%, respectively, in a cohort of 480 children less than 5 years in Togo and Benin (Gong et al. 2002, 2003). Collectively, these studies have provided not only early associations between aflatoxin exposures and possible growth impairments but also a framework for future studies. We conducted a school-based cross-sectional study in Kenya, East Africa to determine AFs exposure using biomarkers, and evaluate their association with nutrition and growth outcomes.

Materials and methods

Setting of the study

In this cross-sectional study, we examine the extent of AFs exposures among children aged 6 to 12 years widespread over two geographic locations. Study participants were recruited from Siaya and Makueni Counties of Kenya, East Africa. The selection of Makueni and Siaya Counties was based on a previous serological survey of AFs exposure levels; which reported higher AFs exposures in Makueni County while Siaya's exposure levels were below the level of detection among adolescents and adults aged 16 to 64 years (Yard et al. 2013). Makueni County lies in Kenya's former Eastern Province while Siaya County forms one of the six counties in the former Nyanza Province (Wangia et al. 2019a). Makueni County is a known hotspot for AFs exposures where deaths from aflatoxicosis have been previously reported (United States CDC 2004; Lewis et al. 2005). On the contrary, no prior documentation of AFs either in food supplies or human biological specimens have been reported in Siaya County. The choice of Makueni and Siaya Counties as study locations provide control for differences in weather conditions, (i.e. Makueni is arid with average rainfall of ~500 mm while Siaya averages ~800 mm in rainfall annually); ethnicity and genetic variabilities, (i.e. Makueni is inhabited by the Bantu ethnics groups of Akamba and Nilotic Luo in Siaya) and lastly, variation in poverty levels where Makueni poverty levels is at 64% and Siaya is at 46%. Detailed description of study setting is provided in the study protocol (Wangia et al. 2019a).

Study participants

The study protocol underwent ethical reviews by the joint ethics committee at the University of

Nairobi and University of Georgia and was granted approval referenced P741/12/2017. Stratified random sampling was used to identify and select different schools per constituency in the two counties. Inclusion criteria for schools included no feeding programmes to guarantee that all meals were provided in the home, and to further limit the possibility of consuming commercially purchased food supplies. School administrations of selected schools were requested to convene a meeting with parents and or guardians of children attending the school at a convenient time and location. The meetings were open to the public and community leaders were in attendance. The study purpose and significance were explained to school officials, teachers, support staff and parents at the meetings, which were presided by the chairperson of parents and teachers' association of each respective school. All questions and concerns were addressed during the meeting, before subject recruitment, and during the study. Full disclosure of study details was given to all participants before informed consent forms were administered. Parents who filled out informed consents were invited to complete a five-part questionnaire that collected demographic information, socio-economic indicators, farming practices, household dietary patterns, and health status of family members. Parents were asked to provide the name and class of their children only if their children were healthy with no current medication and were aged between 6 and 12 years. After the meeting, the researchers cross-checked all forms for accuracies and compiled a list of children as provided by the parents. We only contacted children whose parents had provided prior consent for assent. A child could refuse study procedures without consequence even if their parents had provided prior consent. Children who wanted to be part of the study without parental consent were turned down to their disappointment. Height, weight and mid upper arm circumference measurements were obtained. In addition, phlebotomists withdrew 6–8 ml of venous blood which was separated into sera for aflatoxin biomonitoring.

Laboratory analyses

AFB_1-lysine adducts, a validated biomarker for AFs exposure in human populations was quantified using High Performance Liquid Chromatography with Fluorescence Detection as previously reported (Wang et al. 2001; Scholl et al. 2006; Qian et al. 2010). Thawed human serum samples were placed in 56 ° C water bath for 30 minutes to deactivate any pathogens present. Serum albumin and total protein were quantified as previously detailed (Qian et al. 2013; Kang et al. 2015). An aliquot of 150 µl serum samples were digested by Pronase in the ratio1:4; Pronase: total protein, for 3 hours in a water bath maintained at 37 ° C. The samples were then loaded onto an Oasis Max cartridge from Waters Co. (Milford, Ma, USA) and purified via solid phase extraction over a vacuum chamber manifold. The cartridge was sequentially washed and eluted with 2% formic acid in methanol. The eluents were evaporated to dryness and reconstituted with 150 µl 25% methanol prior to HPLC injection. HPLC analysis was carried out on a 1200 liquid chromatography system (Agilent Technologies Wilmington, DE, USA), at excitation/emission of 470/405 nm. Chromatographic separation was achieved using Zorbax Eclipse XDB-C18 column (5 µm particle size, 250 × 4.6 mm). The mobile phase consisted of 20 mM ammonium phosphate monobasic (pH 7.2) and 100% methanol to achieve separation within 25 minutes at flow rate of 1.0 ml/min. The detection limit of this method is 0.4 pg/ml. For every injection, 100 µl of processed samples were used. AFB_1-lysine binds to blood albumin to a significant extent following metabolism with high stability in human serum when stored properly (Wang et al. 2001; Scholl et al. 2006; Qian et al. 2010). Final AFB_1-lysine concentration in albumin was obtained by manual integration and calculated using calibration curves then adjusted for albumin content.

Statistical analyses

Characteristics of the study population were stratified by county and summarised with proportions for categorical variables and with median and interquartile ranges (IQR) for continuous variables. Distribution of AFB_1-lysine adduct by county was summarised as both continuous (geometric mean and median) and categorical variables (proportion). Weight for age z-score (WAZ), Height for

age Z-score (HAZ) and Weight for Height Z-score (WHZ) were determined in reference to the World Health Organisations (WHO) Multicenter Growth Reference. This reference included children from a diverse set of countries including Brazil, Ghana, India, Norway, Oman and the USA (WHO 1986; de Onis and Onyango 2008). The Multicenter Growth Reference provides considerable built-in ethnic, genetic and cultural variation in regard to how children are nurtured, which further strengthens the standards' universal applicability. We used "zscorer" R package to calculate child anthropometry z-score based on the WHO Child Growth standard. Detailed nutritional information collected was used to calculate a composite dietary diversity score included in the multivariate linear regression models. Specifically, the questionnaire collected highly specific information on dietary intake and food frequency which included 24-h dietary recall, weekly, monthly and yearly estimates of different food groups. Respondent data included detailed information on 1) cereal and grain products; 2) starchy roots and tubers; 3) protein sources; 4) Legumes; 5) Vegetables; 6) Fruits; 7) Oils and Fats; 8) Sugar/Sugar cane products; 9) Dairy Products; and 10) Beverages and Additional Food products which was used to determine a composite dietary diversity score for each household. We used Kruskall Wallis, t-tests and chi-square tests to evaluate the associations between log AFB_1-lysine and all variables. We performed univariate linear regression to estimate the crude coefficient between log AFB_1-lysine adduct and multiple children's growth indicators (weight, height, body mass index (BMI), mid-upper arm circumference (MUAC), height-for-age-Z-score (HAZ), BMI-for-age-Z-score (BAZ), weight-for-age-Z-score (WAZ), mid-upper arm circumference-for-age -Z-score (MAZ)).

We performed multiple linear regression to estimate adjusted coefficient between AFB_1-lysine adduct and growth indicators (weight, height, BMI, MUAC, HAZ, BAZ, WAZ, MAZ). AFB_1-lysine adduct, child-related variables (age of child, sex, wean start at month, the number of meals per day, feel hungry when go to bed, giving snack, and eat after bed time), and other variables (age of mother, age of mother when having the first child, the number of children, marital status, education level, living condition, house's wall, roof type, family size, income, mothers' occupation, spouse's occupation, smoking/alcohol use, grow corn, pesticide fertiliser use, corn storage, aflatoxin knowledge, identify aflatoxin, flour content, source of flour, food source, cost of food affect purchases) were considered for final model selection. We determined variables to include in our final models with lowest AIC values using stepwise algorithm in both directions. If the final models have not included AFB_1-lysine adduct, we would add this variable to explore the relationship between AFB_1-lysine adduct and multiple growth indicators in order to determine the association between child-related variables and multiple growth indicators.

Specifically, multivariate model for weight was adjusted for county, age of child, eat after bedtime, age of mother, age of mother when she had first child, marital status, mother's education, living condition, mother's occupation, ability to identify aflatoxin and flour contents. Multivariate model for height was adjusted for age of child, giving snack, marital status, mother education, flour contents, source of flour. Multivariate model for BMI was adjusted for county, age of child, age of mother, age of mother when she had first child, living condition, family size, mother's occupation; Multivariate model for MUAC was adjusted for county, age of child, No. of meals/day, Eat after bedtime, House's wall, cost of food affect purchases; Multivariate model for HAZ was adjusted for county, age of child, giving snack, marital status, mother's education, flour content, source of flour; Multivariate model for BAZ was adjusted for county, age of child, giving snack, age of mother when she had first child, living condition, and mother's education; Multivariate model for WAZ was adjusted for county, age of child, go to bed and feel hungry, age of mother when she had first child, marital status, living condition, and mother's education, identify aflatoxin. Multivariate model for MAZ was adjusted for county, age of child, no. of meal/day, eat after bedtime, age of mother when she had first child, mother's occupation, identify aflatoxin and if cost of food affected purchases.

AFB_1-lysine was not normally distributed and therefore, the Log AFB_1-lysine was used in all univariate, bivariate and multivariate analyses. Log AFB_1-lysine adducts was used as continuous

variables in multiple linear regression models. In Siaya County, 484 participants were enrolled mainly due to greater mobilisation efforts by the ground team, prior participation in previous research efforts and generally greater involvement in community-led initiatives, compared to lower participation of 327 recruited from Makueni. In statistical analyses, missing entries and incomplete data were excluded from analyses and thus values in Tables may not add up to 811. Multiple imputation was used strategically in sensitivity analyses to address incomplete data and missing entries (Schomaker and Heumann 2014). The total number of children who assented to study procedures are 746, less than our proposed 786 determined in the study protocol (Wangia et al. 2019a). The level of significance was set at p-value ≤ 0.05. SAS v9.4 (Cary, NC) and R version 3.6.1 (Vienna, Austria) statistical tools were used for data cleanup and analyses.

Results

Baseline characteristic of children in the study population stratified by county of residence is detailed in Table 1. Overall, 54.1% of children enrolled in the study were female. The sex distribution was different per county with more male children, 49.8% enrolled from Makueni County compared to Siaya at 43.2%. The median age of children enrolled in the study is 9 years, Inter Quartile Range (IQR) (8, 11) years.

Of 811 children, 63 had data missing in both weight and height. Of 748 with available weight and height information, the median weight and height of the children enrolled in the study were 28 kg and 135.6 cm, respectively. The proportion of children weighing less than 28 kg and shorter than 135 cm was 44.12% (330/748) and 48.66% (364/748) respectively. As shown in Table 1, there are significant differences between all variables in the two separate counties 600 miles apart.

Aflatoxin exposure is predominant and widespread in the areas of study. All children had detectable levels of AFs in serum, range 0.65–518.9 pg/mg albumin and Geometric mean 10.5 pg/mg albumin (95%CI 9.4–11.7). Higher exposures reported among children recruited from Makueni county, Geometric mean 14.03 pg/mg albumin (95%CI 12.50, 15.74) is significantly higher than Siaya's 8.2 pg/mg albumin (95%CI 7.6, 8.8), $p < .001$. These data in a subset of children corroborates previous studies that human exposure to AFs is more prevalent in Makueni compared to Siaya.

Controlling for variables in the five-part questionnaire, among all children, from Siaya and Makueni aged 6–12 years, with every increase of log AFB_1-lysine adducts, Weight-for-age z-score (WAZ) decreases by −0.13, p-value = 0.019, Height-for-age z-score (HAZ) increases by 0.10, p-value = 0.069, which is marginally significant while weight-for-height- z-score (WHZ) increases by 0.03 is not significant, p-value = 0.818. When stratified by county, there are significant decreases in WAZ (−0.08, p-value = 0.044) among children recruited from Makueni county. Aflatoxin exposures had no significant effect on WAZ among children recruited from Siaya County. The effect

Table 1. Characteristics of children in the study population by county.

Characteristics		Overall N %	Makueni (N = 327) N %	Siaya (N = 484) N %	p-value
Sex	Male	372 (45.9)	163 (49.8)	209 (43.2)	0.062
	Female	439 (54.1)	164 (50.2)	275 (56.8)	
Age	6	97 (12.0)	44 (13.6)	53 (11.0)	0.012
	7	82 (10.2)	40 (12.4)	42 (8.7)	
	8	105 (13.0)	37 (11.5)	68 (14.1)	
	9	120 (14.9)	42 (13.0)	78 (16.1)	
	10	134 (16.6)	41 (12.7)	93 (19.3)	
	11	115 (14.3)	44 (13.6)	71 (14.7)	
	12	153 (19.0)	75 (23.2)	78 (16.1)	
Height	Median (IQR)	135.6 (124.9 to 153.1)	136.1 (126.1 to 154.0)	135.2 (124.0 to 152.4)	0.021
Weight	Median (IQR)	28.0 (25.0 to 35.0)	28.0 (23.2 to 33.2)	29.0 (25.0 to 35.0)	0.033
BMI	Median (IQR)	15.6 (13.5 to 17.9)	14.8 (13.1 to 16.8)	16.1 (14.3 to 18.3)	<0.001
MUAC	Median (IQR)	18.0 (17.0 to 20.0)	18.0 (17.0 to 20.0)	18.0 (17.0 to 20.0)	0.023
Height-for-Age -Z score (HAZ)	*Low	77 (10.4)	16 (5.0)	61 (14.4)	<0.001
	+Normal	542 (72.9)	246 (77.1)	296 (69.8)	
	#High	124 (16.7)	57 (17.9)	67 (15.8)	
BMI-for-Age-Z score (BAZ)	*Low	77 (10.4)	16 (5.0)	61 (14.4)	<0.001
	+Normal	542 (72.9)	246 (77.1)	296 (69.8)	
	#High	124 (16.7)	57 (17.9)	67 (15.8)	
Weight-for-Age -Z score (WAZ)	*Low	77 (10.4)	16 (5.0)	61 (14.4)	<0.001
	+Normal	542 (72.9)	246 (77.1)	296 (69.8)	
	#High	124 (16.7)	57 (17.9)	67 (15.8)	
MUAC-for-Age -Z score	*Low	77 (10.4)	16 (5.0)	61 (14.4)	<0.001
	+Normal	542 (72.9)	246 (77.1)	296 (69.8)	
	#High	124 (16.7)	57 (17.9)	67 (15.8)	

*Low = z-scores < −2, +Normal = z-scores ≤−2≥+2, #high = z-scores > +2

Table 2. AFB_1-lysine and growth indicators among children in Kenya 2018.

Growth parameters	†All Children 6–12 years, (*p*-value)	Siaya County, (*p*-value)	Makueni, County (*p*-value)	Overall <9 years, (*p*-value)	Siaya < 9 years, (*p*-value)	Makueni < 9 years, (*p*-value)
Weight-for-Age-Zscore (WAZ)	−0.13 **(0.019)**	0.03, (0.686)	−0.08, (**0.044**)	**−0.11**, (**0.049**)	−0.07, (0.479)	−0.04, (0.546)
Height-for-Age-Zscore (HAZ)	0.10 (0.069)	−0.05, (0.625)	0.03, (0.769)	−0.08, (0.337)	**−0.27**, **(0.049)**	0.13, (0.224)
Weight-for-Height-Zscore (WHZ)	0.03 (0.818)	0.12, (0.598)	−0.01, (0.354)	−0.17, (0.437)	0.01, (0.970)	−0.12, (0.651)

of aflatoxin exposures on HAZ is only significant among children below 9 years with a decreasing HAZ of −0.27, *p*-value 0.049. All growth parameters decreased among children less than 9 years with increasing log AFB_1-lysine adducts. Detailed data is shown in Table 2.

Even though stunted children (HAZ < −2 = Low) from Siaya County had high AFB_1-lysine adducts in serum as shown in Figure 1, children recruited from Makueni county had significantly higher AFB_1-lysine adducts, GM = 14.03 pg/mg albumin vs Siaya's 8.2 pg/mg albumin. Underweight children (WAZ < −2 = Low) in Makueni County have the highest AFB_1-lysine adducts as shown in Figure 2. Moreover, children with low BMI- for age-Z-score (BAZ < −2 = Low), and low mid-upper arm circumference (MUAC < −2 = Low) in Makueni County had the highest aflatoxins exposure (Figures 3 and 4). Collectively, these data confirm that children with high aflatoxin exposures were more likely to suffer some form of growth impairments.

Discussion

Dietary exposure to aflatoxins is widespread in both Siaya and Makueni counties among children between the ages of 6 to 12 years. Overall, about 67.6% of the children had AFB_1-lysine adducts exceeding 5.0 pg/mg of albumin, geometric mean (GM) 10.5 pg/mg albumin (95% CI 9.4–11.7). In a study conducted in Uganda among children below 3 years, AFB_1-lysine adducts were slightly lower with GM 9.7pg/mg (95% CI 8.2–11.5) (Asiki et al. 2014). Another recent study in Makueni County of Kenya among children between the ages of 1 to 14 years in Makueni County reported two times higher exposure levels, geometric mean of 20.4 pg/mg albumin (Githang'a et al. 2019). Similarly, in Gambia, aflatoxin-albumin adducts among children 6 to 9 years geometric mean 22.3 pg/mg, (95%CI 20.3–24.5) (Turner et al. 2003). Taken together, these studies indicate that children are more likely to have higher bio-availability of aflatoxin metabolites compared

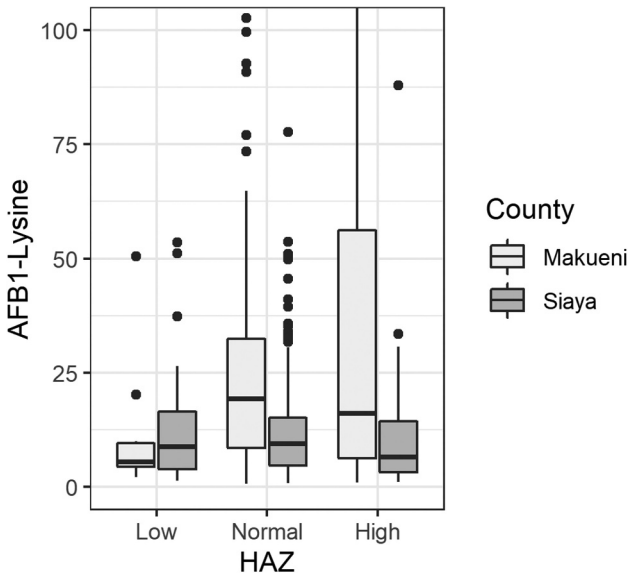

Figure 1. AFB1-lysine adducts and Height for Age Z-score (HAZ) *Low = HAZ <-2; Normal = HAZ >= -2<=+2; High = HAZ > +2

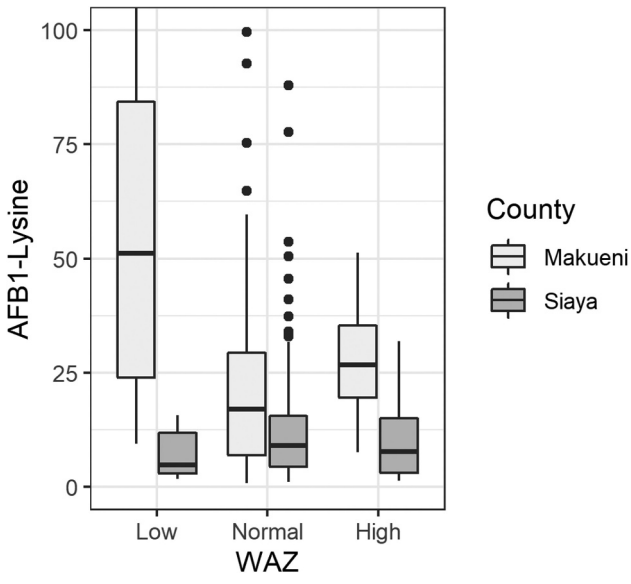

Figure 2. AFB1-lysine adducts and Weight for Age Z-score(WAZ) >*Low = WAZ <-2; Normal = WAZ >= -2<=+2; High = WAZ > +2

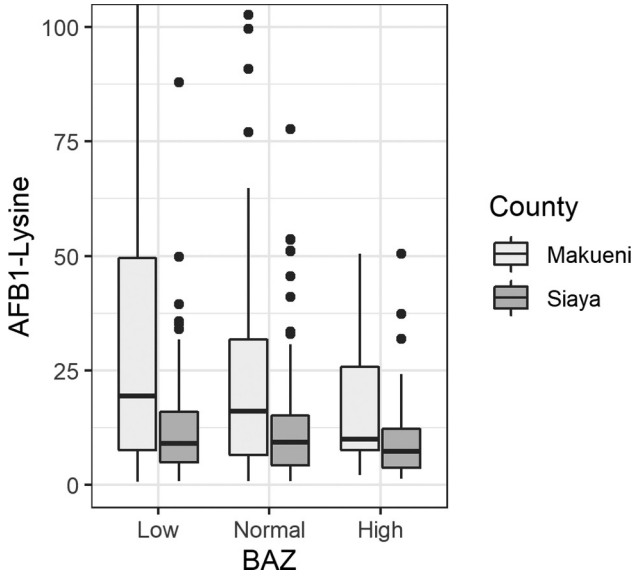

Figure 3. AFB1-lysine adducts and BMI- for Age Z-score (BAZ)"*Low = BAZ <-2; Normal = BAZ >= -2<=+2; High = BAZ > +2"

to adolescents and adults. Toxicant exposure levels are relative to body weight and thus, expected to be higher in children compared to adults, which is partly attributed to limited capacity for detoxification for xenobiotics including AFs among children with developing organs.

Dietary exposure to AFs and other mycotoxins has been implicated in malnutrition and growth impairment in children. Moreover, younger children between the ages of 6 to 9 years appear to suffer worse growth and nutrition outcomes. In the current study, among children 6 to 9 years, WAZ decreases by −0.11 (−0.54, −0.01), p-value = 0.049.

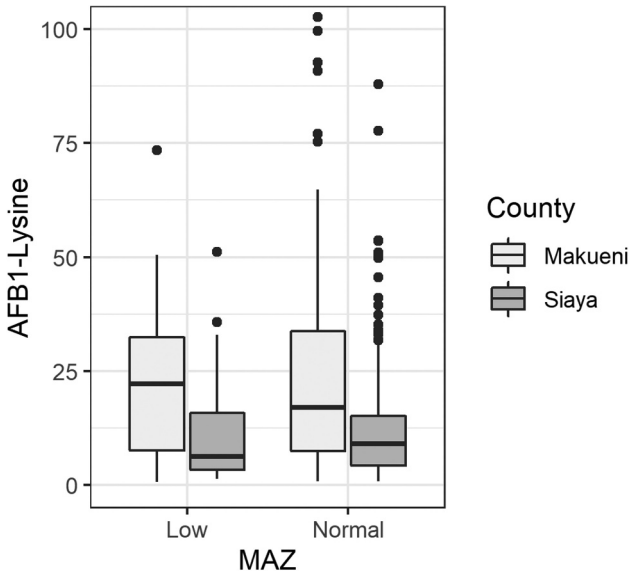

Figure 4. AFB1-lysine by Mid-Upper-Arm-Circumference-for-Age-Z-score [MAZ]%„*Low = MAZ <-2; Normal = MAZ >= -2<=+2; High = MAZ > +2

Likewise, a different study reported a significant association between AF exposure and wasting, p = .002 among children less than 3-years old in Kenya. This study however quantified AFs in weaning flours, which was used a proxy for AF exposure (Okoth and Ohingo 2004). A different study in Kenya among children 6 to 9 years, found a significant association between AF-albumin adducts and impaired child height after adjusting for age, sex and possible schistosomiasis infection status; the growth faltering was attributed to altered expressions of the insulin-like growth factor genes P = .052. (Castelino et al. 2015).

In another study conducted in Kenya, growth reduction estimation for children below 3 years exposed to AFM_1 from milk in average have an effect of −0.34 on HAZ, contributing a total of 2.7% of childhood stunting (Ahlberg et al. 2018). In Benin, a significant negative association between height velocity, but not weight, and mean AF- albumin levels were reported in an 8-month longitudinal study in 200 children below 3 years (Gong et al. 2004). Moreover, a difference of 1.7 cm over the 8-month study period in adjusted height between the highest and lowest AF-albumin quartile was observed (Gong et al. 2004). Following 138 Gambian neonates for 1 year, Turner et al. reported that reducing maternal exposure to AFs from 110 to 10 pg/mg could result in weight increase by 800 g and height increase by 2 cm on average (Turner et al. 2007). In a Nigerian study by McMillan et al, a significant correlation between HAZ and AFB_1-lysine supports the causal role of AF and stunting (McMillan et al. 2018).

On the contrary, a number of studies have also reported no association between AFs exposure and growth impairments. A cohort study in Gambia among 472 older children between 6 and 9 years old did not report any association between AF exposure and HAZ or WAZ; however, a weak association was reported for WHZ, an indicator for wasting (Turner et al. 2003). Likewise, in Cameroon, a study conducted of 220 children between the ages 1.5 to 4.5 years reported no association between the different malnutrition categories namely stunted, wasted and underweight with mycotoxin exposure (Njumbe Ediage et al. 2013). Furthermore, in a longitudinal study completed in Tanzania with 166 children between the ages of 6–14 months, a negative association between AF-albumin and

stunting did not reach statistical significance, even though co-exposure with fumonisins was implicated in growth impairments (Shirima et al. 2015). In another Tanzanian cohort study of children, there was no association between AFs exposure and stunting, underweight or wasting/thinness among children less than 3 years, however, significant negative association was reported between urinary fumonisins, stunting and underweight (Shirima et al. 2015; Chen et al. 2018). Similarly, a different longitudinal study completed in Nepal, AF exposure in children less than 3 years was not associated with stunting, underweight, and thinness/wasting (Mitchell et al. 2017). In a cluster randomised control trial done in Meru County of Kenya, reducing AF exposure by providing households with non-contaminated corn lowered AFs serum levels of pregnant women by 27% (Hoffmann et al. 2015, 2018), however, this reduction was not associated with improved linear growth. Taken together, these studies demonstrate the importance of controlling for confounding factors to delineate the pervasive nature of AFs exposures especially children's health, and more importantly, the need of mechanistic studies. Further studies to evaluate specific thresholds under which toxic AF metabolites contribute to immune modulation, disruption of intestinal barrier and interference with growth axis are timely and warranted. In summary, dietary exposure to AFs is widespread; however, their role on children's growth impairment is not conclusive.

Conclusions

In developing countries, malnutrition is one of the most pervasive risk factors for human morbidity and mortality. Stunting, wasting and underweight are major indicators of continuing malnutrition and have been associated with chronic aflatoxin exposure. These parameters are well-established risk markers for poor child development with significant consequences that last beyond childhood years. The current study adds to the mounting evidence on the role of AFs and other mycotoxins in malnutrition and growth impairment among children. The effect is adverse in children due to limited detoxification capacity of xenobiotic and higher sensitivity of growth inhibitory effects at a younger age. In order to sufficiently address chronic malnutrition and growth impairments, efforts must be put in place to control for mycotoxin exposure to as low as reasonably achievable.

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ORCID

Ruth Nabwire Wangia-Dixon http://orcid.org/0000-0002-0730-2867

Declaration of interest

The authors declare no potential or actual conflicts of interest.

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