Child development in rural Burkina Faso

Association between maternal alcohol consumption, stunting, schooling, and neuropsychological outcomes

Anselme Siméon Sanou

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Dedication

To my lovely daughter

Believe in the Almighty God, dream and do things to be happy. I love you so much.

Scientific environment

Four African partners – Makerere University (Uganda), University of Zambia, University of Western Cape (South Africa) and Centre Muraz (Burkina Faso) – and three European partners – the Centre for International Health (CIH) at the University of Bergen (Norway) Université de Montpellier (France) and Uppsala University (Sweden) - formed a research consortium in 2004 called "Promoting Infant health and nutrition in Sub-Saharan Africa: Evaluation of safety and effectiveness of major interventions (PROMISE)". In Burkina Faso, several studies were conducted including the PROMISE Exclusive breastfeeding (EBF) in 2004-2010, PROMISE Safety and efficacy of infant peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding (PEP) in 2009-2013, PROMISE Helping Babies Breathe (HBB) in 2012-2013 and PROMISE Saving Brains (SB) in 2012-2015, and PROMISE Mechanisms and Safety (M&S) in 2016-2018.

This thesis is based on the analysis of data from the Burkina Faso site of the follow-up study of the PROMISE EBF cohorts in Uganda and Burkina Faso called PROMISE Saving Brains (SB). This project was a multi-centre study in Uganda and Burkina Faso funded by Grand Challenges Canada and led by Professor James K. Tumwine from Makerere University, with the Principal Investigator in Burkina Faso being Professor Nicolas Meda from Centre Muraz. The aim was to assess the effect of peer-counselling for exclusive breastfeeding (EBF) in the first 6 months of life on cognition at 6-8 years and other determinants of human capital formation, including: behavioural and emotional status; school readiness and attainment; health status; fine and gross motor skills; physical growth; and household economic status.

This thesis has been part of a collaboration between:

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Norway

Centre MURAZ Research Institute,
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Abbreviations

CCT-1	Children's Category Test Level 1
CIH	Centre for International Health
CNS	Central Nervous System
EBF	Exclusive breastfeeding
ECD	Early Childhood Development
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorder
GDP	Gross Domestic Product
GPS	Global Positioning System
HIV	Human Immunodeficiency Virus
KABC-II	Kaufman Assessment Battery for Children second edition
MPI	Mental Processing Index
PROMISE	Promoting Infant health and nutrition in Sub-Saharan Africa: Evaluation of safety and effectiveness of major interventions
SB	Saving Brains
SD	Standard Deviation
SDG	Sustainable Development Goals
TOVA	Test of Variable of Attention
UNICEF	United Nations Children's Fund
WHO	World Health Organization
Z	Notation for standard deviation

Abstract

Introduction: The general aim of this thesis was to evaluate the association of maternal alcohol consumption, stunting (low height-for-age) and schooling on neuropsychological outcomes among children in rural Burkina Faso based on data from the Burkina Faso's site of the PROMISE Saving Brain's study.

Methods: The thesis is based on data collected from the PROMISE Saving Brain study, a follow-up study of a community-based cluster-randomized trial on promotion of exclusive breastfeeding. Children were re-enrolled at age 6-8 years in Uganda and Burkina Faso. In the site of Burkina Faso, a total of 561 children were alive, traced and re-consented to participate in the evaluation of neuropsychological outcomes. The Kaufman Assessment Battery for Children, 2nd edition (KABC-II), the Children's Category Test Level 1 (CCT-1), and the Test of Variable of Attention (TOVA) have been used. Effect size differences using Cohen's d and linear regression were used to analyse any associations. The theoretical framework of the 2016 Lancet series was used to categorize all the variables. In a final analysis, we included all the variables in one single analysis.

Results: Children whose mothers reported alcohol consumption during pregnancy performed significantly more poorly for the KABC-II sub-tests 'Atlantis' (adjusted coefficient = -4.61, p = 0.02), 'Number recall' (adjusted coefficient = -0.54, p = 0.04), and for 'Triangle' (adjusted coefficient = -0.61, p = 0.03), and scored a significantly higher number of errors at CCT-1 (adjusted coefficient = 2.5, p = 0.002). Stunted children performed significantly less well in KABC-II general cognition ($p \leq 0.0001$), TOVA 'attention' (p = 0.04), and scored a significantly higher number of errors for CCT-1 'cognitive flexibility' (p = 0.02), and for TOVA 'inhibition' (p = 0.02). On the TOVA test, children not in school performed significantly worse for 'Response time' ($p \leq 0.0001$), 'Response time variability' ($p \leq 0.0001$), 'Errors of omission' (p = 0.001), 'Errors of commission' (p = 0.003) and 'D prime score' ($p \leq 0.0001$) compared to children in school. In the multivariable model with all the different variables including 17 neuropsychological outcomes, schooling was associated with 12 of the

neuropsychological outcomes ('Atlantis', 'Conceptual thinking', 'Face recognition', 'Story completion', 'Rover', 'Triangle', 'Word order' 'General cognition', 'Total Response Time', 'Total Response Time Variability', 'Total errors of omission' and 'D prime score'), stunting was associated with 04 neuropsychological outcomes ('Atlantis', 'Triangle', 'General cognition', and 'D prime score'), and maternal alcohol consumption during pregnancy was associated with 04 neuropsychological outcomes ('Triangle', 'Word order', 'General cognition' and CCT-1).

Conclusion: Assessing neuropsychological performances among children with many risk factors is complex. This thesis may have found some significant associations between maternal alcohol consumption during pregnancy, stunting and schooling, and poorer neuropsychological performances of children aged 6-8 years but cannot conclude on any causal relations. More structured studies with prospective collection of exposure data are needed to demonstrate causal relationships. However, this thesis shows the importance and the challenges of studying neuropsychological performances in multi-risk contexts and highlights the need for continuous promotion of child development to support children to reach their developmental potential.

List of publications

1. Sanou AS, Diallo AH, Holding P, Nankabirwa V, Engebretsen IMS, Ndeezi G, Tumwine JK, Meda N, Tylleskar T, Kashala-Abotnes E. Maternal alcohol consumption during pregnancy and child's cognitive performance at 6–8 years of age in rural Burkina Faso: an observational study. PeerJ. 2017 Jun 30;5:e3507.

2. Sanou AS, Diallo AH, Holding P, Nankabirwa V, Engebretsen IMS, Ndeezi G, Tumwine JK, Meda N, Tylleskar T, Kashala-Abotnes E. Association between stunting and neuro-psychological outcomes among children in Burkina Faso, West Africa. Child and Adolescent Mental Health and Psychiatry 2018;12:30.

3. Sanou AS, Diallo AH, Holding P, Nankabirwa V, Engebretsen IMS, Ndeezi G, et al. Effects of schooling on aspects of attention in rural Burkina Faso, West Africa. PloS One. 2018;13(9):e0203436

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To my lovely wife and our precious 5 year-old daughter: you have provided me with a family life beyond all possible dreams. Thank you very much. I love you.

Definition of concepts

Brain development: This is a prolonged process that begins in the third gestational week with the differentiation of the neural progenitor cells, and extends at least through late adolescence, arguably throughout the lifespan (1).

Child development: This is the period of physical, cognitive and social growth that begins during pregnancy, goes to birth and continues through early adulthood (2).

Early Childhood Development (ECD): This refers to the physical, cognitive, linguistic and socio-emotional development of a child from the prenatal stage up to age 8 (3).

Cognitive function: This refers to the mental abilities used to engage in different aspects of everyday life. Cognitive function encompasses memory, language, and visuospatial and executive functions (4).

Executive function: This is one such cognitive ability that involves higher level management of a broad set of processes, including working memory, problem solving, planning prospective actions, attention and multitasking (5).

Neuropsychological assessment: This is a procedure used to evaluate the behavioural and functional expression of brain dysfunction, and identify the impact of brain injury or disease on the cognitive, sensorimotor, emotional and general adaptive capacities of an individual (6).

Fetal alcohol spectrum disorder (FASD): This is an umbrella term used to describe individuals who experience disability as a result of prenatal alcohol exposure (7).

Stunting: This is defined as a length/height z score, 2 standard deviations below the WHO median (8). It refers to linear growth retardation (9).

Winsorizing: This is the limitation of extreme values by replacing their values with the nearest scores within this range to discount the influence of outliers (10).

1. Introduction

1.1. Background information

1.1.1. Theories on child development

Middle childhood defined as ages 6 to 12 is a time when children develop foundational skills for building healthy social relationships and learn roles that will prepare them for adolescence and adulthood (11,12). Several developmental theories involving middle childhood were described. Those theories include psychoanalytical theories, behavioural and social learning theories, cognitive theories, developmental system theories. In the psychoanalytical theories, Sigmund Freud described the psychosexual theory (13) and Erik Erikson described the psychosocial theory (14); in these theories, beliefs focus on the formation of personality, where children move through various stages, confronting conflicts between biological drives and social expectations. Behavioural theories were described by John Watson (15) and B.K. Skinner (16), and the social learning theory was described by Albert Bandura (17); in these theories, beliefs focus on the importance of the environment and nurturing the growth of a child. In cognitive theories, Jean Piaget described the cognitive development theory and its stages (18), and Lev Vygotsky described the socio-cultural theory (19). In these theories, beliefs focus on a description of how children learn; they also include the information processing theory, which uses the model of the computer to describe how the brain works. The developmental systems theory was extensively described by Uris Bronfenbrenner with the ecological systems (20). The belief tries to explain that development cannot be done by a single, but rather by a complex system. In the system theories, Sara Harkness described the developmental niche (21), and Arnold Sameroff described the transactional model (22) and the unified theory of development (23). More specifically to Africa, indigenous africans believed that children played critical roles in their own development, and had a responsibility for their self-education; this was later influenced by the introduction of Islamic/Arabic and Western traditions in Africa (24). Developmental stages in African contexts were also described, emphasising that the content was influenced by different contexts, including culture (25,26).

1.1.2. Risk factors of poor child development

The second paper of the 2007 Lancet series on Child development describes the risk factors that affect child development, which should be the main focus for interventions. The risk factors include socio-cultural, biological and psychosocial risks, and have been described as contributing to adverse outcomes in child brain development (27). Psychosocial risk factors include, for instance, maternal depression, neglect, and exposure to violence and harsh parenting. Biological risk factors include, for instance, infectious diseases, nutrient deficiencies, toxic exposures and restrictions in prenatal and postnatal growth. Socio-cultural risk factors include reduced access to services (hospitals and schools), low maternal education and gender inequity (27). Nevertheless, risks were individually considered in the paper; children are frequently exposed to cumulative and multiple risks. Development is increasingly compromised as risks accumulate. In 2010, ~249 million children under 5 years of age were at risk of poor development in 141 countries, and 81% were at risk of poor development in Sub-Saharan Africa (Figure 1) (28). Burkina Faso is a Sub-Saharan African country that has multiple risk factors and where children are at risk of poor development (28). Major advances in neuroscience show that different factors, such as maternal exposures, stunting or schooling affect brain structure and function, compromising child development and subsequently a developmental trajectory; timing, dose and differential reactivity influence how factors affect brain development (29).

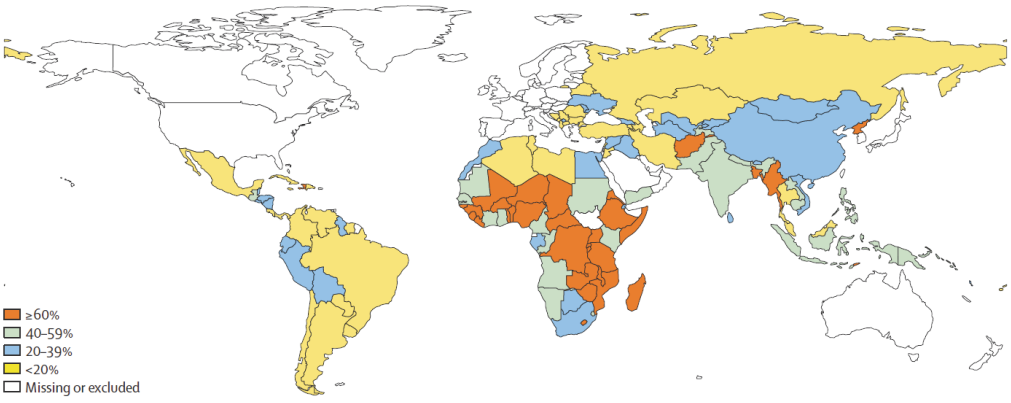

Figure 1: Prevalence of children at risk of poor development in 141 countries in 2010 (Lu C et al. (28)).

1.1.2.1. Maternal alcohol consumption

Alcohol consumption during pregnancy is a risk factor in several diseases and injury conditions (30,31). Alcohol consumed during pregnancy may interfere the developmental progression of the fetus, which will results in physical and central nervous system damage that has multiple lifelong consequences on health. The damage leads to fetal alcohol spectrum disorder (FASD), which includes fetal alcohol syndrome (FAS) and neuro-developmental disorder related to alcohol (7,32). FASD affects people from all socio-economic backgrounds, including their families. Individuals with FASD need lifelong assistance in several services, including community, health and education; it has an economic effect in the society (33).

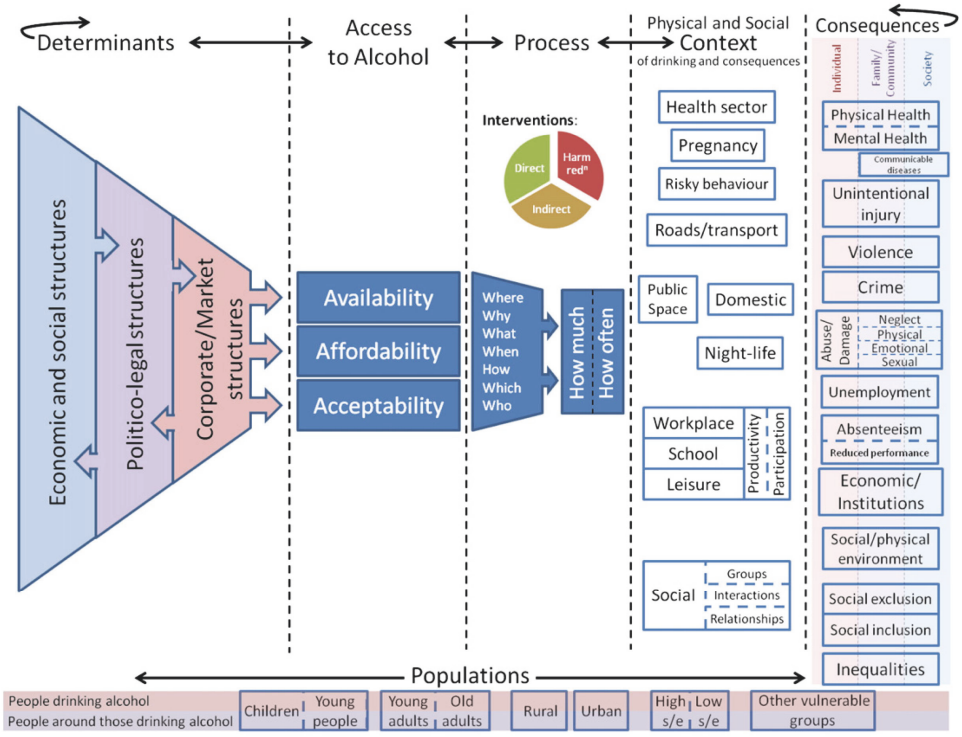

Figure 2: Conceptual framework of drivers and outcomes of alcohol consumption (Martineau F (34)).

The conceptual framework of alcohol consumption (Figure 2) presents the pathways connecting proximal determinants to distal outcomes. The consequences of alcohol consumption include health related outcomes at individual, family and society level;

those consequences seem to be related to accessibility of alcohol, the quantity and the frequency of consumption. The determinants include economic, social, politic and legal factors (34).

1.1.2.2. Stunting

Poor nutrition among children is a major risk factor in several diseases and disabilities (29,35–38). Stunting refers to chronic under-nutrition, reflecting retardation in linear growth and cumulative growth deficits in children (27,39). It is a good indicator of child a well-being and an accurate reflection of social inequalities (40). Stunting affects >165 million children in the world, 85 million children in low-income countries (28), and is highly prevalent from 20 to 35% in Sub-Saharan Africa (38,41). Its prevalence remains high in sub-Saharan African countries (42).

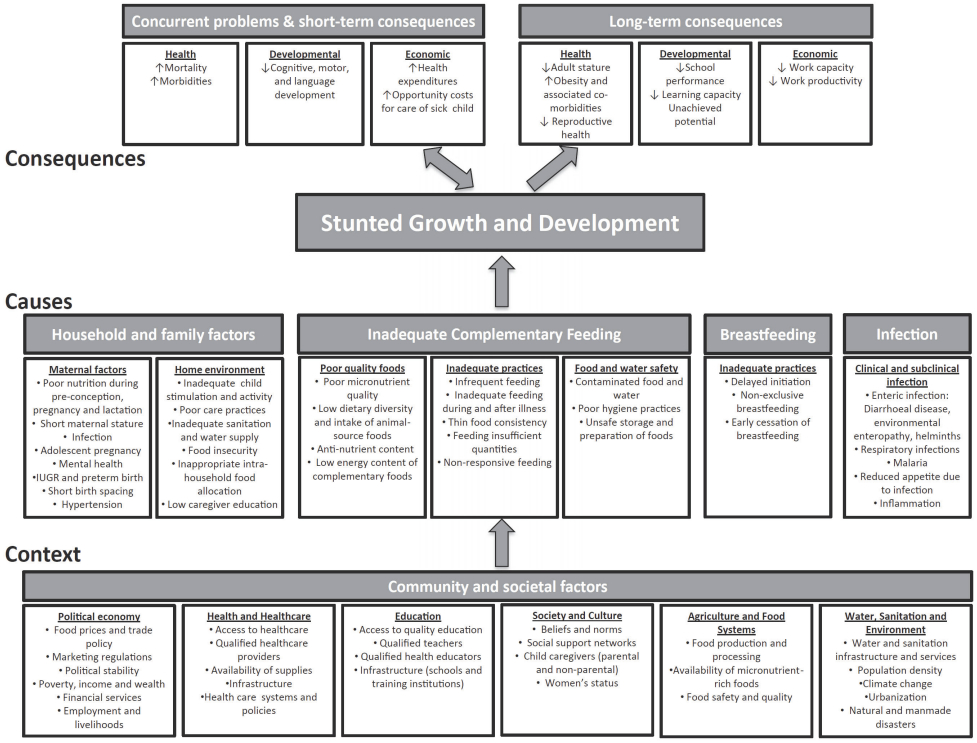

Figure 3: WHO conceptual framework on Childhood Stunting (Stewart C (43)).

The WHO conceptual framework on childhood stunting (Figure 3) presents the context, causes and consequences of stunting. The proximal part of the framework

describes the concurrent problems and short-term consequences of stunting which include high mortality and morbidity, low cognitive, motor and language development, high health expenditures and cost for care of sick child. It also describes the long term consequences of stunting which include low school performance and low learning capacity. The middle part of the framework presents potential causes of stunting which include household and family factors, inadequate complementary feeding, breastfeeding and infections. The distal part of the framework presents the context of stunting which includes community and societal factors (43).

1.1.2.3. Schooling

Attending school is important in child development, and is associated with health and increased earnings later in life (44,45). It has a strong impact on health, survival and development; children who do not complete school or repeat grades are at the greatest risk of sub-optimal development (46,47). However, 59 million school-age children do not receive formal education worldwide (48,49), with sub-Saharan Africa having the lowest rate (50).

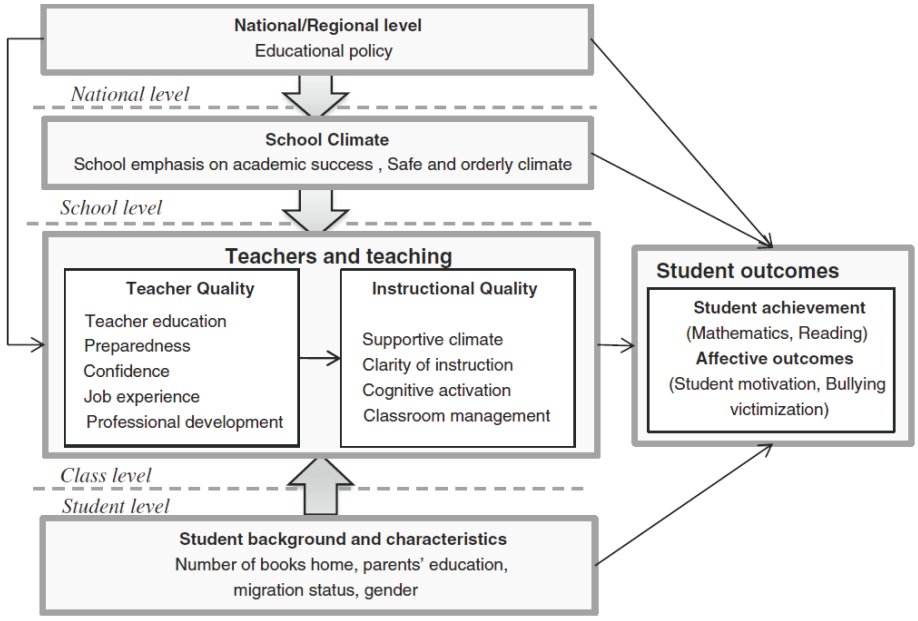

Figure 4: Conceptual framework of determinants of student outcomes (Nilsen T (51)).

The conceptual framework of determinants of student outcomes (Figure 4) focuses on relations between the national level, school level, class, and student level. The framework shows the influence of national, school and teacher level to student outcomes (51). The relations may be direct or indirect given the differences between cultures, educational policies and systems. The Heckman curve shows that the highest rate of economic returns comes from schooling and early investments in children (52).

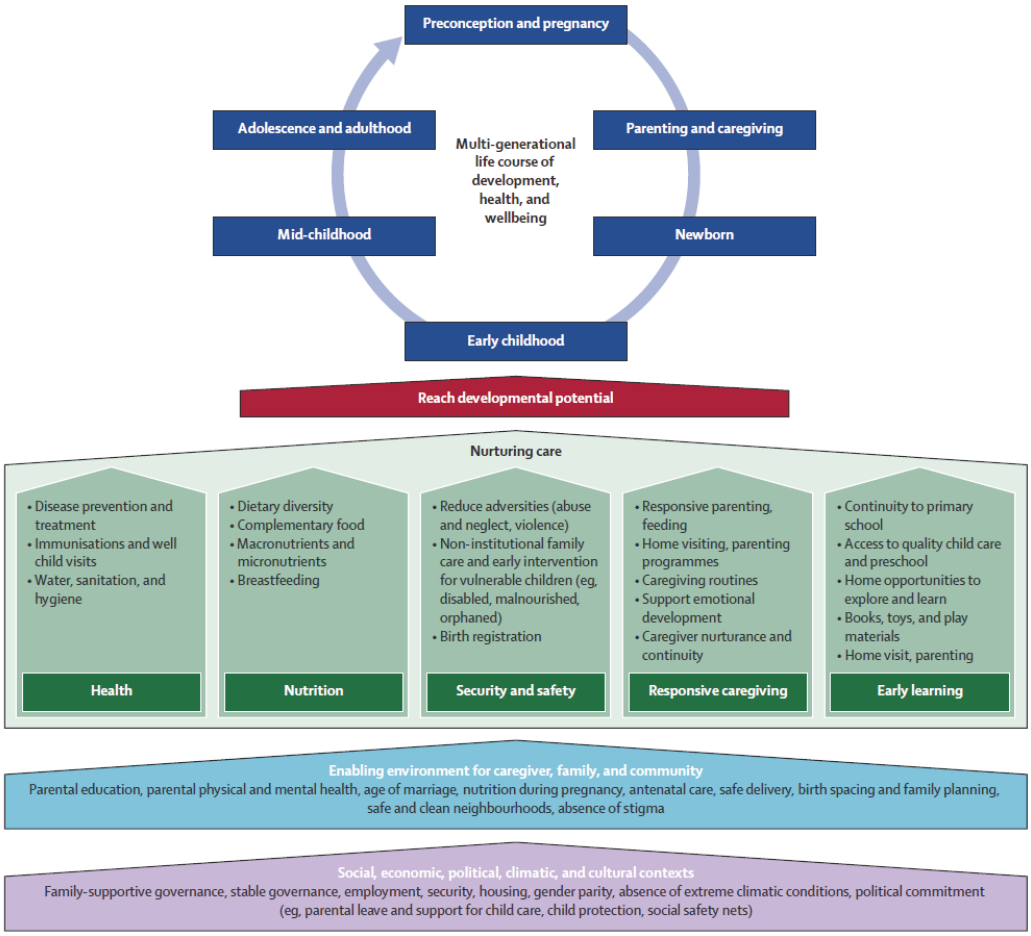

Figure 5: Conceptual framework of child development (Black MM (53)).

1.1.3. Theoretical framework to reach developmental potential

The 2016 Lancet series offer an interactive and holistic framework for understanding the factors and interventions that influence child developmental potential; it emphasised that children maximize their potential when they are protected, well nourished, have learning opportunities and are given responsive care for development (45,53,54). The different factors that influence child developmental potential are numerous (see Figure 5). In the framework, the end-point is a multi-generational life-course of development, health and wellbeing. This life-course that goes from preconception and pregnancy to adolescence and adulthood is affected by a range of different factors and interventions at different levels.

The most immediate factors influencing developmental potential are nurturing care composed of 5 groups, namely health, nutrition, security and safety, responsive care-giving, and early learning. Considering the framework, lack of responsive care-giving, such as alcohol consumption during pregnancy, lack of good nutrition, conditions such as stunting, or lack of learning (such as not going to school) influence child development. Child development is also affected by intermediate factors, such as the environment for the care-giver, family and community. The most distant factor in the framework is the context; it includes social, economic, political, climatic and cultural factors (53).

1.2. Prior use of neuropsychological assessment tools KABC-II, CCT-1 and TOVA in Africa

Selecting a test for neuropsychological assessment is challenging in Africa due to the unavailability and adapted norms for African populations, low levels of literacy or cultural and language inappropriateness (55).

In this thesis, we have used the Kaufman Assessment Battery for Children (2nd edition; KABC-II), the Children's Category Test 1 (CCT-1) and the Test of Variable of Attention (TOVA) to assess the children's neuropsychological outcomes. All 3 are presented in detail in the subjects and methods section (2.5. Outcome measures).

The tests were selected because (1) KABC-II is an individually administered cognitive test with verbal and nonverbal components that has been used across diverse cultural contexts, including Africa (56–59); (2) CCT-1 is a widely used non-verbal test developed to evaluate problem-solving in children; it is fast and easy to administer (60–62); (3) TOVA is an individually administered computerized continuous performance test developed to assess attention in normal and clinical populations (63,64).

1.3. Rationale of the thesis

This thesis stems from the PROMISE Saving Brains (SB) program, which was a follow-up study of the PROMISE EBF cohorts in Uganda and Burkina Faso. The overall objective of the study was to assess the long-term effect of exclusive breastfeeding promotion by peer counsellors in Uganda and Burkina Faso, on cognitive abilities, emotional-behavioural-social symptoms, school performance and linear growth among 5-8 year- old children. The main outcomes have been published (65), showing small and non-significant differences in the outcomes, from which it was and concluded that peer promotion for exclusive breastfeeding in Burkina Faso and Uganda was not associated with differences in cognitive abilities, emotion-behaviour-social symptoms, school performance and linear growth.

During the implementation of the PROMISE SB study, we made some observations. In fact, during the data collection in the field, we observed that several women including pregnant women were drinking alcohol. In our further investigations, we learnt that in Burkina Faso, home-brewing accounts for 84% of the type of alcohol which is consumed (66). The proportion of women who consume alcohol is 30%, which is among the highest in Africa (67); the estimated prevalence of pregnant women who consume any amount of alcohol consumption in the population is 11.3% (68).

The literature review of the effect of alcohol consumption during pregnancy on cognitive outcomes showed divergent conclusions from an association (69,70) to no association (71–75) based on the quantity and the frequency of the consumption. However, the studies were mainly implemented in high-income or middle-income countries such as South Africa where merchandised non-home-brewed alcohol is common (69–77). Little was known on the effects of maternal alcohol consumption during pregnancy on the neuropsychological outcomes in their offspring in the low-income country context where lack of resources, rural areas, presence of several risk factors and home-brewed alcohol are common.

Another observation during the data collection of the PROMISE SB study in the field was the presence of several malnourished children. In our literature review we found that stunting was a public health problem in the country and going from 8% for 10-12 year-old children in Ouagadougou, the capital city (78), to 29% for 1 to 5 year-old children in Kaya, the Central North region (79), and 8-14 year-old children in the Plateau Central (North East) and the Centre-Ouest (Central West) regions (80). The 2018 national survey on nutrition in Burkina Faso showed the prevalence of stunting for 1-5 year-old children was 25% in the country and 27.1% in the Cascades region, our study area (81). Stunted children do not achieve their linear growth potential because of inadequate nutrition, sub-optimal health conditions, etc., and may suffer irreversible cognitive and physical damage (40). It is known to be associated with decreased cognitive function; children who experienced stunting in early childhood may have deficiencies related to cognition, school performance and intelligence deficits (82–93). In 2015, a meta-analysis assessed the association between stunting and child development using data from 58,513 children aged 36-59 months (94). However, little is known on the effect of stunting during the middle childhood period in a African context with its lack of resources, rural areas and the presence of several additional risk factors.

We also observed during the data collection of the PROMISE SB study in the field that many school age children were not at school. In our literature review, we found

that in Burkina Faso, the net attendance ratio of primary school participation is 50% for female and the enrolment ratio of pre-primary school participation is 4% [7]. The educational system is characterized by geographical disparities both in terms of school enrolment ratio and school infrastructure coverage. There are also gender disparities (71% enrolment ratio for boys, compared to 67% for girls). Out-of-school rates of children at primary school age are also high. The situation of preschool enrolment is low, with a ratio at only 4% for both boys and girls (50). Regarding the association between schooling and neuropsychological outcomes, we found that several studies using human administered tests show that neuro-developmental outcomes of children attending school is improved compared to those that were unexposed (95–100). However, there are gaps of knowledge in the association between schooling and neuropsychological outcomes in the context of several risk factors, notably where literacy and school attendance is low, where both human administered and computerised tests are used.

Beside the results of the PROMISE SB study and based on our observations, gaps of knowledge on the effects of maternal alcohol consumption during pregnancy, stunting and schooling on neuropsychological outcomes were identified.
The gaps of knowledge were:

1. There was a scarcity of data on the association between maternal alcohol consumption during pregnancy and a child's neuropsychological outcomes:
    - in Sub-Saharan African countries,
    - in areas where home-brewing alcohol is common,
    - in a context of lack of resources, rural areas and the presence of several risk factors.
2. There was a scarcity of data on the association between stunting and a child's neuropsychological outcomes:
    - during the middle childhood period,
    - in a context of lack of resources, rural areas and the presence of several risk factors.

3. There was a scarcity of data on the association between schooling and a child's neuropsychological outcomes:
    - in a context where literacy and school attendance is low,
    - in a context of lack of resources, rural areas and the presence of several risk factors.

We anticipate that improved information and knowledge in these fields will enhance efforts to promote child development in this country, Africa and the world.

1.4. Objectives and hypotheses of the thesis

The general objective of the thesis was to evaluate the association between maternal alcohol consumption, stunting, schooling and neuropsychological outcomes among children in rural Burkina Faso, based on data from the Burkina Faso site of the PROMISE Saving Brain study. The measurement tools used in the thesis were the one selected by the PROMISE SB study; the reason of the selection is described in chapter 1.2. Prior use of neuropsychological assessment tools KABC-II, CCT-1 and TOVA in Africa.

The specific objectives were:

1. To study the association between maternal alcohol consumption during pregnancy and the offspring's cognitive performance using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II) and the Children's Category Test Level 1 (CCT-1) in rural Burkina Faso (Paper 1).
2. To study the association between stunting and neuropsychological outcomes using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), the Children's Category Test Level 1 (CCT-1) and the Test of Variables of Attention (TOVA) among children in Burkina Faso (Paper 2).
3. To study the association between schooling and attention measures using the Test of Variables of Attention (TOVA) among children in rural Burkina Faso (Paper 3).

After publication the 3 papers, we conducted a single analysis to examine the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and the different neuropsychological outcomes.

Our hypotheses were:

1. Maternal alcohol consumption during pregnancy may be associated with the offspring's cognitive performance,
2. Stunting may be associated with the child's neuropsychological outcomes,
3. Schooling may be associated with the child's attention measures.

The hypotheses were to study the direction in both ways: "negatively" and "positively".

2. Subjects and methods

2.1. Study area

Burkina Faso is a low-income country located in the middle of West Africa; the population resides mainly in rural areas (70% in 2018), and 45% of the population were aged 0-14 years in 2018 (101). The literacy rate is very low and the average years of education attained in women and girls was <3 years in 2013 (102). The official language in Burkina Faso is French (Table 1); however, the country has more than 60 different ethnic groups and languages (103).

Table 1: **Background information of Burkina Faso** (101)**.**

Information	Situation in 2018
Population	20 Million
Capital	Ouagadougou
Official language	French
Crude birth rate	40 births/1,000 population
Crude death rate	9 deaths/1,000 population
Maternal mortality rate	371 deaths/100,000 live births
Infant mortality rate	55 deaths/1,000 live births
Life expectancy at birth	62 years
Health expenditure	5% of GDP
GDP per capita	$1,800
Total fertility rate	4.7 children/woman
Total adults literacy rate	36%
Population growth rate	3%
Total sex ratio	0.99 male/female
Urban population	29.4%
Mother's mean age at first birth	19.4 years
Telephones – mobile cellular	18 Million
Internet users	14 %

Data collection took place in the Cascades Health region (Figure 6, 7 and 8) in the South-West of Burkina Faso, especially in the health districts of Banfora and Mangodara, from 2013 to 2015. The district of Banfora covers an area of 6,300 km^2, with an estimated population of 340,000, and the district of Mangodara has an area of 9,100 km^2, with an estimated population of 200,000 in 2013 (104). Both districts are in

rural areas where children do not have access to technology, e.g. computers, mobile phones or internet. Several local languages are spoken in the study area, including *Gouin*, *Karaboro*, *Dioula*, *Senoufo*, *Turka*, *Moore* and *Fulfulde* (103,105,106). The area has an annual rainfall of 950-1250 mm during a 6-month rainy season (May-October). Farming and animal husbandry are the main activities in the rural areas, and the town of Banfora (population 76,000) is a trading centre (107).

Figure 6: Cascades Health region in the South-West of Burkina Faso (dark blue).

2.2. Study design

The PROMISE Saving Brains study was a cross-sectional study to evaluate neuropsychological outcomes of children from the initial PROMISE community-based cluster-randomized exclusive breastfeeding trial (PROMISE EBF), which subsequently was followed as a cohort (65,106,108).

Figure 7a. Classical village with its conventional architecture.

Figure 7b. Village influenced by foreign architecture.

Figure 7c. Agriculture dominates the landscape.

Figure 7d. Water is channelled to the fields.

Figure 7e. Cotton is a common cash crop.

Figure 7f. Health centre in the area.

Figure 7g. Donkeys are commonly used for transport.

Figure 7h. Bikes are also common for transport.

Figure 7i. An open water well.

Figure 7j. A borehole well.

Figure 7k. The Baobab tree is wellknown in West Africa.

Figure 7l. The city of Banfora.

2.3. Setting and target population

In the initial PROMISE-EBF trial, clusters were mapped out based on criteria of accessibility, population size and health system, and were subsequently randomized by a central coordinating team into intervention and control arms. In total, 24 clusters with an average population size of 1,000 inhabitants were selected (108).

All pregnant women in the study communities were invited to participate in the study and 99% consented to be screened. Overall, 895 pregnant women were enrolled in the initial PROMISE-EBF trial.

2.4. Recruitment and re-enrolment in the PROMISE Saving Brains

Previous databases from the initial PROMISE EBF trial, GPS coordinates, previous community health workers and qualified personnel were used to access children initially enrolled, for their re-inclusion in the current study. During the recruitment

and re-enrolment period, I was in the field with two sociologists to retrieve the children. I had moved to the study site and had access to the different databases and the information to retrieve children. For the identification, all the children from the same village were listed on a paper with their first name, surname, name of the father, name of the mother, date of birth, name of the village, GPS coordinates of the household, name of the community health worker during the previous EBF study. In each village, the community health workers who previously participated to the PROMISE EBF helped us to retrieve the different children. The GPS coordinates of the household, previous document such vaccination card or EBF enrolment ID card was used to confirm the household and the identity of the child (Figure 8).

Out the 794 children who were enrolled in the PROMISE EBF trial and using this process, the PROMISE SB study managed to retrieve 566 children who were alive from 2013 to 2015. Re-consent for inclusion was proposed and 561 parents accepted to be re-included in the PROMISE SB study. The study was conducted in a rural areas with a high degree of social cohesion and low degree of mobility which contributed to the high re-enrollment rate.

2.5. Outcome measures

2.5.1. Kaufman Assessment Battery for Children, 2nd edition (KABC-II)

The KABC-II is an individually administered cognitive test with verbal and nonverbal components (56–59). The selected sub-tests in our study were:

Atlantis: The examiner teaches the child nonsense names for fanciful pictures of fish, plants and shells. The child demonstrates learning by pointing to each picture (from an array of pictures) when it is named. 'Atlantis' is a measure of associative memory, and forms part of the learning ability scale;

- **Conceptual thinking**: The child is presented a set of 4-5 pictures and asked to identify the picture that does not belong with the set. It measures visual and spatial abilities, and forms part of the simultaneous processing scale;
- **Face recognition**: The child looks at a photograph of either one or two faces for 5 seconds and then chooses the correct face (or faces) shown in a different

pose from the original photograph. It measures visual and spatial abilities and forms part of the simultaneous processing scale;

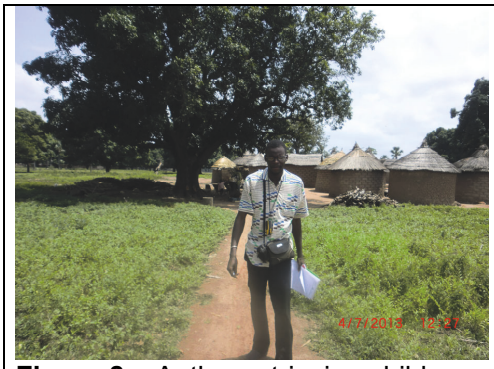

Figure 8a. Author retrieving children in the village with the use of GPS.

Figure 8b. Community mobilisation for the study.

Figure 8c. Author reconsenting the family to participate in the study.

Figure 8d. Community health workers who were familiar with the original PROMISE EBF trial assisted in the interaction with the families.

Figure 8e. KABC-II testing.

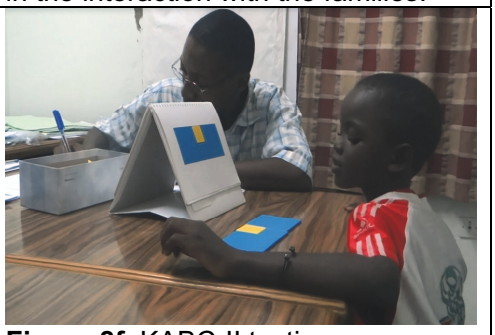

Figure 8f. KABC-II testing.

Figure 8g. KABC-II testing.

Figure 8h. KABC-II testing.

Figure 8i. Conducting the TOVA test.

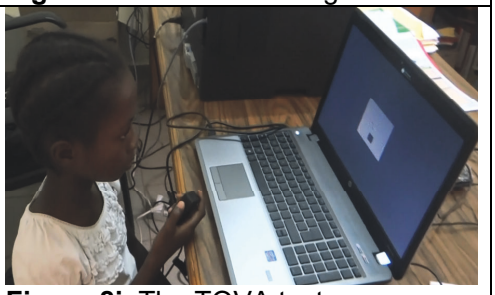

Figure 8j. The TOVA test.

Figure 8k. Measuring weight and height.

Figure 8l. A lunch break for the children who are being tested today.

- **Story completion**: The child is shown a row of pictures that tell a story, with some of the pictures missing. The child should complete the story by selecting the missing pictures from a selection in their correct locations. 'Story completion' measures pattern recognition and reasoning, and forms part of the planning ability scale;

- **Number recall**: The child is asked to repeat a series of numbers in the same sequence the examiner said them. This measures memory span and forms part of the sequential processing scale;
- **Rover**: The child moves a toy dog to a bone on a checkerboard-like grid that contains obstacles (rocks and weeds) and tries to find the path that requires the fewest moves. 'Rover' is a measure of spatial scanning, general sequential or deductive reasoning and number skills, and forms part of the simultaneous processing scale;
- **Triangle**: For most items, the child assembles several identical foam triangles (blue on one side, yellow on the other) to match a picture of an abstract design. For easier items, the child assembles a set of colourful plastic shapes to match a model constructed by the examiner or shown on the easel. 'Triangle' measures spatial abilities and visualization, and forms part of the simultaneous processing scale;
- **Block counting:** The child counts the exact number of blocks in several pictures of stacks of blocks. The stacks are configured such that one of more blocks is hidden or partially hidden from view. 'Block counting' measures reasoning and forms part of the simultaneous processing scale;
- **Word order**: The child touches a series of silhouettes of common objects in the same order as the examiner has named the objects. It measures memory span and forms part of the sequential processing scale;
- **Pattern reasoning**: The child is shown a series of stimuli that form a logical, linear pattern, with one stimulus missing. The child completes the pattern by selecting the correct stimulus from an array of 4-6 options at the bottom of the page. 'Pattern reasoning' measures inductive reasoning, visualization and forms part of the simultaneous processing scale (56,109,110).

2.5.2. Children's Category Test Level 1 (CCT-1)

CCT-1 is an individually administered standardized test for children to test their ability to solve problems on the basis of corrective feedback. CCT-1 was used to examine the effect of different exposures, including health factors (111–119). The total number of

errors is counted at the end of the test, the higher the number of errors, the worse the performance (60,112,120). We used the number of errors to assess the cognitive flexibility.

2.5.3. Visual Test of Variables of Attention (TOVA)

The visual Test of Variables of Attention (TOVA) is an individually administered computerized continuous performance test developed to assess attention (63,64). The test duration is 22 minutes and the total test time (T) is divided in 4 quarters: (Q1-Q4) and 2 halves (H1, where target stimuli are less frequent; and H2, where target stimuli are more frequent). The total score reflects the subject's performance over the entire test. Each target stimulus is presented for 100 ms every 2 seconds. In total, 324 target stimuli are presented during the entire test. The target is presented in 22.5% (n = 72) during the first half of the test (stimulus infrequent condition 1) and 77.5% (n = 252) during the second half (stimulus frequent condition 2) (121). We used the following variables to measure attention:

- **Response time** (in milliseconds): this is a measure of the average time it takes for the subject to respond correctly to a target. It is considered as a measure of speed of responding and the reactivity of the subject. A shorter 'Response time' equates with a faster speed of responding and a swifter reactivity of the subject.
- **Response time variability**: this score is a measure of the variability in the subject's response time regarding accurate responses; it is considered as a measure of consistency in the speed of responding. The shorter the 'Response time variability', the more consistent is the performance of the subject.
- **Errors of omission:** this score is measured as the failure to respond to the target stimulus. 'Errors of omission' scores are a measure of inattention. Fewer 'Errors of omission' equates with less inattention in the subject.
- **Errors of commission**: this score is measured as an inappropriate response to the non-target stimulus. 'Errors of commission' scores are a measure of impulsivity. The higher the 'Errors of commission', the more impulsive is the subject's behaviour.

- **D prime score**: this is a response sensitivity score that can be interpreted as a measure of accurate performance over time. The higher the 'D prime score', the greater the accuracy of the subject over time (63,64,122,123).

A summary of the methods of calculation and a description of the scores is presented in Table 2.

Table 2: **Calculation methods and score description in the TOVA test.**

Score	Calculation methods	Calculation formula*	Description
Total response time	Average of the correct response times	$\frac{\sum(\text{Correct Response Times})}{\#\ \text{Correct Responses}}$	Measure of speed of responding and the reactivity
Total response time variability	Standard deviation of the mean correct response times	$\sqrt{\frac{(\sum_{i=0}^{n}(x_i - \text{Mean Correct RT})^2)}{(\ \#\ \text{Correct Responses}\ )}}$	Measure of consistency in the speed of responding
Total errors of omission	Number of correct responses to the stimuli	$\frac{\#\ \text{Omissions}}{(\#\ \text{Targets} - \#\ \text{Anticipatories})} x100$	Measure of inattention
Total errors of commission	Number of incorrectly responses to the no- stimuli	$\frac{\#\ \text{Commissions}}{(\#\ \text{NonTargets} - \#\ \text{Anticipatories})} x100$	Measure of impulsivity
D prime score	Accuracy of stimuli and non-stimuli discrimination	$z\left(\frac{\text{Commission Percentage}}{100}\right) - z\left(1 - \left(\frac{\text{omission Percentage}}{100}\right)\right)$	Accurate performance over time

*All the calculations are done by the computer and the results are directly given

2.5.4. Assessment procedures

The assessments (KABC-II, CCT-1 and TOVA) were conducted by 4 psychologists who spoke at least one of the main local dialects (*Gouin, Karaboro,* and *Dioula*), and were recruited and trained for the study. They lived in the study area and received regular supervisory visits from the coordinator and the local investigators of the PROMISE SB. The children were randomly assigned to the psychologists for assessment. TOVA was the first test to be administered to the child, followed by KABC-II and CCT-1 during a one-to-one session. The instructions of the tests were translated only in *Dioula,* given the assumption that all the children could speak the language. However, the team recruited was able to speak the other languages and understood the local context; they were then able to interact with the children in other languages.

For TOVA, the children sat in a quiet room at ~75 cm away from a laptop. TOVA Version 8.1 was use, presented on Hp Probook 4540s laptop computers in which Windows 8 had been installed. These laptops have 15.6 inch screens for a clear view of the stimuli. The children were instructed to respond by pressing a hand-held micro-switch whenever a target stimulus appeared, and not to respond when a non-target stimulus was shown on the screen (Figure 9) (63). Each stimulus was randomly presented for 100 milliseconds every 2 seconds.

The psychologists underwent field training and refresher training to standardize the way to administer the assessments on local children prior to the study participants.

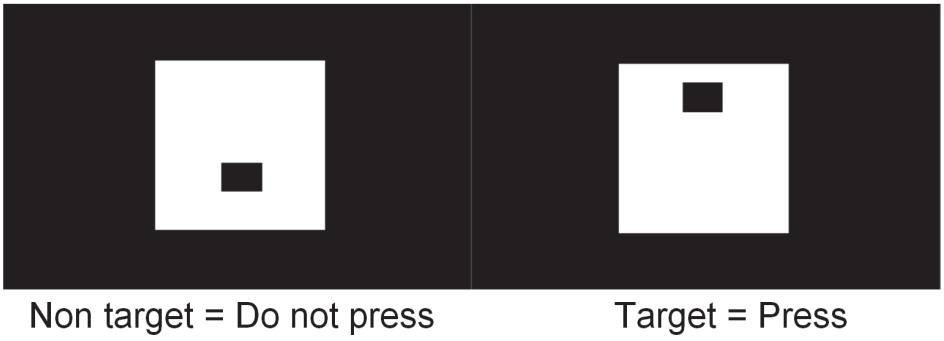

Figure 9: Screenshots of non-target and target stimuli in visual TOVA (63).

We used KABC-II and CCT-1 for paper 1 and TOVA for paper 3 as they were considered the most appropriate for these papers. After the publication of the paper on alcohol on 30 June 2017, the submission of the paper on schooling on 18 August 2017, and during the process of analyzing the data of the paper on stunting, it was realized that it was most appropriate to include all 3 tests in the paper on stunting. All the 3 tests were then included in the paper on stunting and submitted on 14 October 2017.

2.6. Measures of exposure

The main exposures were maternal alcohol consumption during pregnancy, stunting and schooling.

Information about maternal alcohol consumption during pregnancy was collected retrospectively during a household interview with the caretaker prior to the neuropsychological assessment. Data collectors approached each child's household to administer a questionnaire to the caregiver during a one-to-one interview. Mothers were the primary respondents. A simple yes/no answer was asked for regarding any alcohol consumption during pregnancy.

Stunting, the second exposure, required a trained person to measure anthropometric variables (weight, height, age) at the study site prior to the neuropsychological testing and according to standard procedures (124). We defined stunting as a height-for-age 2 standard deviations (SD) below the mean. We calibrated the stadiometer according to the instructions of the manual. WHO Anthro was used to classify the children into height-for-age categories of nutritional status (8).

Information about schooling (child attends school? Yes/No) was collected in a household interview with the caretaker in the same week and prior of the neuro-cognitive assessment. Data collectors approached each child's household to administer a questionnaire to the caregiver during a one-to-one interview. Mothers were the primary respondents, and responses were verified at the school.

To calibrate and standardize all the instruments, field-testing and piloting was conducted before the start of data collection.

2.7. Analytical framework with all variables

For this thesis, we have used the 2016 Lancet series theoretical framework as an illustration to categorize all the variables including the main exposures, the confounders and the outcomes into the different sections (Figure 10).

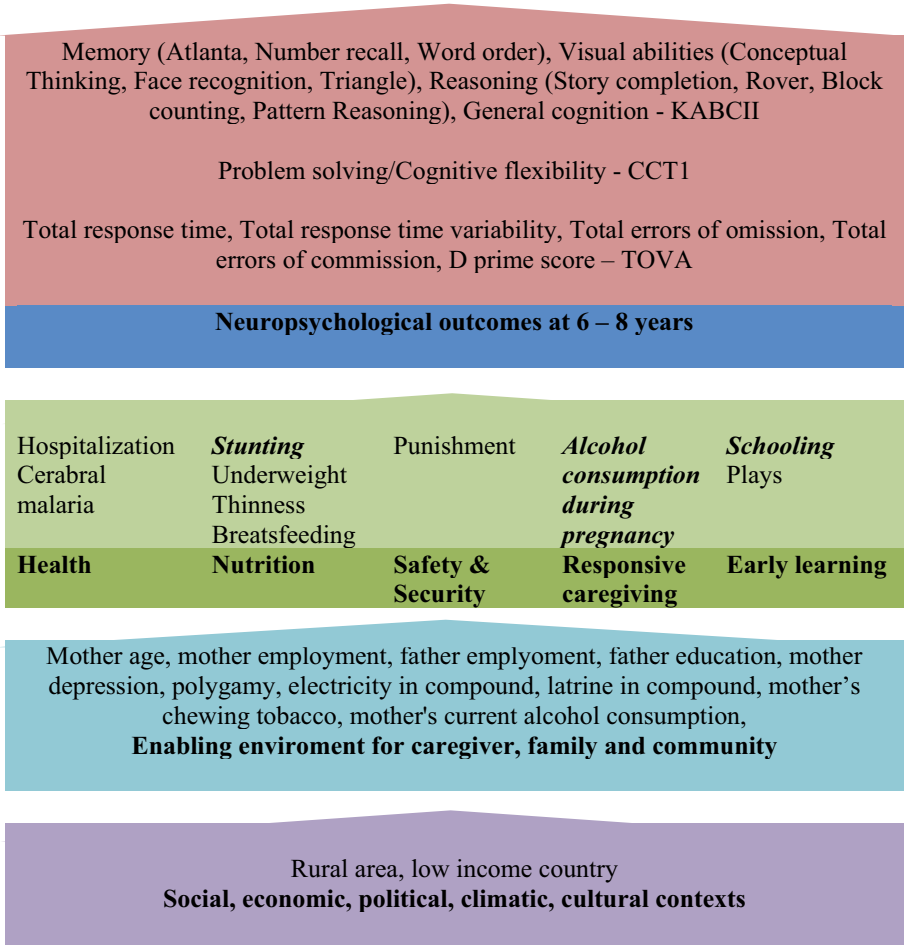

Figure 10: Analytical framework including effects of main exposures and confounders on neuropsychological outcomes.

2.8. Data management and statistical analysis

2.8.1. Data management

Data, except for TOVA, were collected on paper case-report forms that were entered in the study database using Epidata 3.1 (www.epidata.dk). Data from the TOVA were extracted from the computer and added to the dataset. Data required from the previous PROMISE EBF database were retrieved.

2.8.2. Statistical analysis

Statistics were analysed in several stages:

1. To examine within-population variance of the tests, the distribution of scores (mean, standard deviation, median, minimum and maximum) were used. Box-and-whisker plots per exposed and unexposed groups were used to illustrate the children's performances on the different tests (KABC-II, CCT-1 and TOVA). Extreme scores were winsorized to discount the influence of outliers by replacing their values with the nearest scores within this range.
2. To examine the internal consistency reliability of items of the tests,
    a. In paper 1, split-half reliability coefficients were calculated for KABC-II (56,59) and Cronbach's alpha coefficient was calculated for CCT-1 (60,112,120). The level of significance of the reliability coefficient was $p \geq 0.7$.
    b. In paper 3, Pearson product-moment coefficients (r) were computed; these assess the degree of agreement between the test portions; they were appropriate for measuring the reliability for timed tasks, such as the TOVA (63).
3. To examine the association between the exposures and the outcome measures, effect size differences using Cohen's d (125,126) were calculated, and analysed by linear regression. Analyses were conducted with standardized and un-standardized scores in the papers, whereas for the synopsis only standardised scores were used.
    a. In paper 1, we conducted the analysis between maternal alcohol consumption during pregnancy as main exposure and KABC-II including

'Atlantis' – memory, 'Number recall' – memory, 'Triangle' - spatial abilities, 'Block counting' - reasoning, 'Conceptual thinking' - visual abilities, 'Face recognition' - visual abilities, and also CCT-1 errors - problem solving.

b. In paper 2, we conducted the analysis between stunting and KABC-II 'General cognition', subtests measuring reasoning, memory, spatial abilities, CCT-1 'Cognitive flexibility', TOVA 'Attention', and TOVA 'Inhibition'. As highlighted in paper 2, not all subtests of KABC-II were used because of the low internal consistency in paper 1. The selected KABC-II subtests, with good internal consistency, were 'Atlantis', 'Number Recall', 'Conceptual Thinking', 'Face Recognition', 'Triangle' and 'Block Counting'.

c. In paper 3, we conducted the analysis between schooling and TOVA 'Total response time', 'Total response time variability', 'Total errors of omission', 'Total errors of commission', and 'D prime score'.

4. To examine the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) on 17 neuropsychological outcomes, we used 3 multivariable regression analysis models on standardized scores for KABC-II, CCT-1 and TOVA using the command `mvreg` in Stata:

   a. Model 1 was a global analysis of the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) on 17 neuropsychological outcomes without any other confounding factors of the analytical framework. All the neuropsychological outcomes from KABC-II, CCT-1 and TOVA were examined followed by a joint analysis of the exposures to account for a joint multiple comparison of the outcomes.

   b. Model 2 was a global analysis of the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) on 17 neuropsychological outcomes adjusted for all the confounding factors of the analytical framework. For the environment

condition, the confounding factors were mother's age, mother's employment, father's employment, father's education, mother's depression, polygamy, electricity in the compound, latrine in the compound, mother's chewing tobacco, and mother's current alcohol consumption. For the child nurturing care condition, the confounding factors were hospitalization and cerebral malaria for health, underweight, thinness and exclusive breastfeeding for nutrition; for safety and security, the confounding factor was punishment; and for early learning, the confounding factor was play. The children were all from a rural area in Burkina Faso. All the neuropsychological outcomes from KABC-II, CCT-1 and TOVA were examined followed by a joint analysis of the exposures to account for a joint multiple comparison of the outcomes.

c. Model 3 was a global analysis of the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) on 17 neuropsychological outcomes adjusted for statistically significant confounding factors. All the neuropsychological outcomes from KABC-II, CCT-1 and TOVA were examined.
d. For each model, a multivariable analysis was conducted for each outcome; this means that 17 analyses were conducted in model 1, 17 analyses were conducted in model 2 and 17 analyses were conducted in model 3.
e. For each of the neuropsychological outcomes, all the confounding factors of the analytical framework were initially included and progressively deleted using a backward elimination of the most insignificant variable. The main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) were forced to be in the model.

STATA 13 was used for the analysis; a summary of the methods is given in Table 3.

2.9. Ethical considerations

Written informed consent was obtained from all care-takers in the study, and oral assent was obtained from the children. The study was approved by the Institutional Review Board of Centre MURAZ number 008-2013/CE-CM.

Table 3: Summary of the methods used in the papers and thesis.

	Paper 1	Paper 2	Paper 3	Thesis
Exposure measure	Maternal alcohol consumption during pregnancy	Stunting	Schooling	All exposures (Maternal alcohol consumption during pregnancy, Stunting, Schooling)
Outcome measure	Atlantis, Conceptual thinking, Face recognition, Story completion, Number recall, Rover, Triangle Block counting Word order, Pattern reasoning, CCT-1 errors	Memory, Visual abilities, Spatial abilities, Reasoning, General cognition, Cognitive flexibility, Attention, Inhibition	Total response time, Total response time variability, Total errors of omission, Total errors of commission, D prime score	All outcomes (Atlantis, Conceptual thinking, Face recognition, Story completion, Number recall, Rover, Triangle, Block counting Word order, Pattern reasoning, CCT-1 errors, Total response time, Total response time variability, Total errors of omission, Total errors of commission, D prime score
Test used	KABC-II, CCT-1	KABC-II CCT-1 TOVA	TOVA	KABC-II, CCT-1, TOVA
Internal consistency reliability	Split-half reliability and Cronbach's alpha coefficient		Pearson product-moment coefficients	
Association analysis	Cohen's d effect size and linear regression, using unstandardized and standardized scores	Cohen's d effect size and linear regression, using unstandardized and standardized scores	Cohen's d effect size and linear regression, using unstandardized and standardized scores	Multivariables regression using standardized scores

3. Results

3.1. Characteristics of the population

A comparison of the socio-demographic characteristics of the 794 participants in the preceding PROMISE EBF trial between the participants who were alive and re-enrolled in the PROMISE SB study and those who had died or moved out showed that the groups were similar. In the data of the previous PROMISE EBF trial, the presence of electricity in the compound was 87.5% (489/559) for enrolled children of the PROMISE SB, 84.1% (122/145) for children who had passed away, and 88.6% (78/88) for children who had moved out. Similarly, the presence of toilet in the compound was 52.9% (295/558) for enrolled children, 42.8% (62/145) for children who had passed away, and 47.7% (42/88) for children who had moved out. The age of the mothers was 26.2 (±6.3) for enrolled children, 25.3 (±6.8) for children who had passed away, and 24.3 (±6.9) for children who had moved out.

Of the initial 794 enrolled children in the PROMISE EBF trial in Burkina Faso site, 561 were alive, traced and re-consented to participate in the follow-up study. An appalling number of 145 children (18.3%) had died (figure 11). The attrition in the remaining cohort was 88 children, 13.6%. The overall attrition was 233 children, 29.3%. We compared the baseline socio-demographic characteristics of participants who were re-enrolled and not and found no significant differences. In total, 554 children completed the KABC-II and the CCT-1, and 534 completed the TOVA. Out of the 566 children who were alive and in the area during the study, one family declined to participate and 4 had travelled, the total rate of re-inclusion was 99.1% (561/566).

Out of the 561 children who were re-included in the study, 554 children were assessed for KABC-II/CCT-1 and 534 for TOVA. The response rate was good, with 98.7% (554/561) for KABC-II/CCT-1 and 95.2% (534/561) for TOVA. The completion rate was also good with 93.5% (518/554) for KABC-II/CCT1 in paper 1, 96.0% (532/554) for KABC-II/CCT1, 96.1% (513/534) for TOVA in paper 2, and 100% (534/534) in paper 3 (Figure 11).

Of the children, 51.7% (268/518) were boys, 49.4% (256/518) were at school, 15.8% (80/518) were stunted, and 18.5% (96/518) had a mother who self-reported alcohol consumption. The mean (± standard deviation, SD) age of children at assessment was 7.2±0.4 years (Table 4).

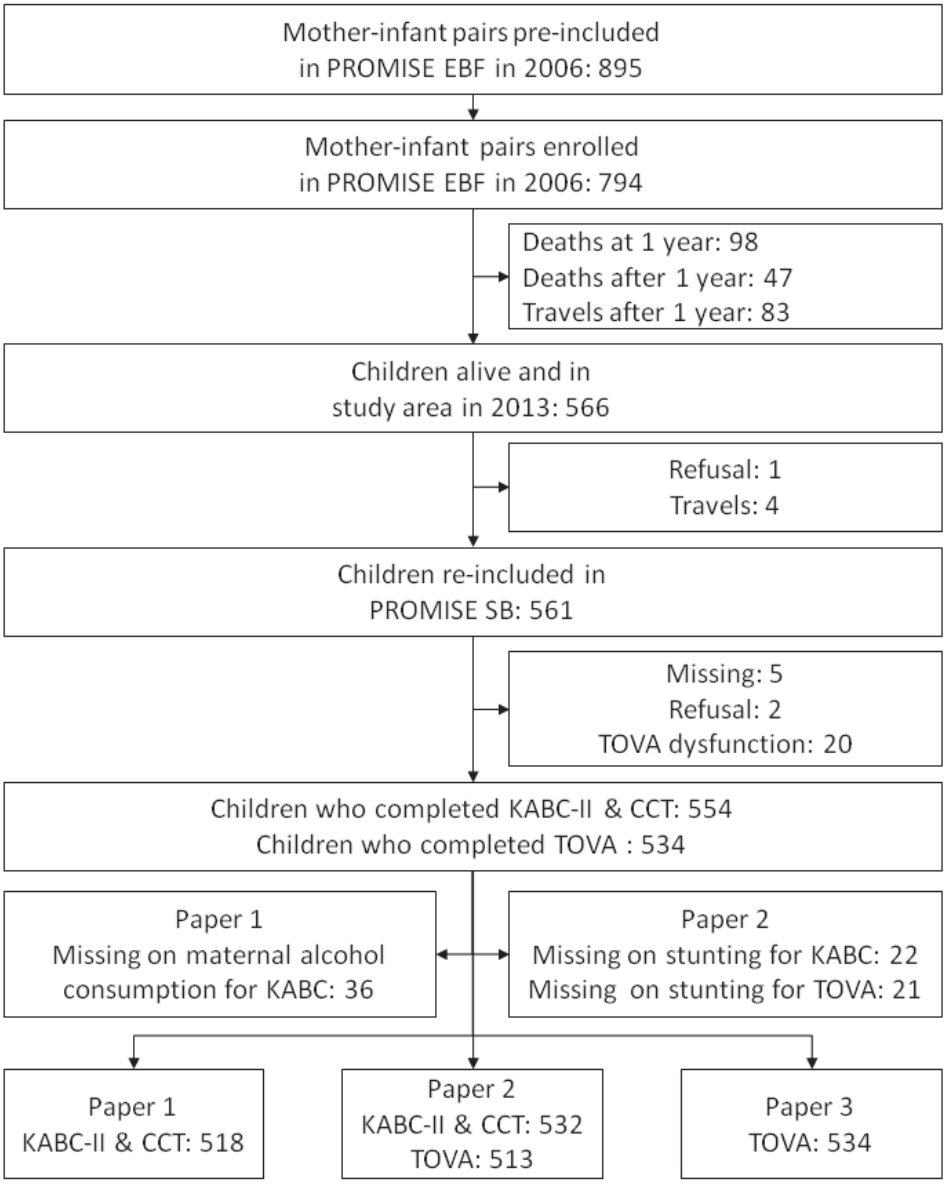

Figure 11: Study profile.

Table 4: **Description of the children who completed the KABC-II, CCT-1 and TOVA from the PROMISE SB study in rural Burkina Faso from 2013 to 2015.**

	N=518
Maternal alcohol consumption	
No	422 (81.5)
Yes	96 (18.5)
Stunting	
No	426 (84.2)
Yes	80 (15.8)
Schooling	
No	262 (50.6)
Yes	256 (49.4)
Sex of the child	
Boys	268 (51.7)
Girls	250 (48.3)
Child had been hospitalized	
No	391 (77.9)
Yes	111 (22.1)
Father educated	
Yes	156 (30.6)
No	354 (69.4)
PROMISE EBF intervention	
Control arm	274 (52.9)
Intervention arm	244 (47.1)
Mother employed	
Yes	26 (5.0)
No	492 (95.0)
Mother chewing tobacco	
No	495 (95.6)
Yes	23 (4.4)
Mother depressed	
No	267 (52.6)
Yes	241 (47.4)
Latrine in the compound	
Yes	380 (73.4)
No	138 (26.6)
Child has history of cerebral malaria	
No	428 (92.0)
Yes	37 (7.9)
Child plays with object at home	
No	271 (52.3)
Yes	247 (47.7)
Child received punishment in last 12 months	
No	494 (95.4)
Yes	24 (4.6)
Electricity in the compound	
Yes	399 (77.0)
No	119 (23.0)
Underweight (< -2 SD in weight-for-age)	
No	456 (89.9)
Yes	51 (10.1)
Thinness (< -2 SD in BMI-for-age)	
No	487 (96.4)
Yes	18 (3.6)
Polygamy (father has more than 1 wife)	
No	186 (36.0)
Yes	331 (64.0)
	Mean ± SD
Child's age, mean ± SD (in years)	7.2 ± 0.4
Mother's age, mean ± SD (in years)	33.4 ± 6.3

3.2. Paper 1: Maternal alcohol consumption during pregnancy and child's cognitive performance at 6-8 years of age in rural Burkina Faso: An observational study

In Paper 1, we investigated the association between maternal alcohol consumption during pregnancy and child's cognitive performance at 6-8 years of age in rural Burkina Faso.

We found that children whose mothers reported alcohol consumption during pregnancy performed significantly poorer regarding memory ('Atlantis' and 'Number recall') and spatial ability ('Triangle') tests, with a small to moderate effect size difference compared to children whose mothers had not consumed alcohol during pregnancy. The effect size difference was small for 'Atlantis' (0.27) and 'Triangle' (0.29), and moderate for 'Number recall' (0.72). The children exposed scored a significantly higher number of errors with a small effect size (0.37) at problem solving (CCT-1) test compared to unexposed children.
For some visual ability tests, no effect size differences were found for 'Conceptual thinking' (0.02), 'Face recognition' (0.10), 'Story completion' (0.05). No effect size differences were found for some reasoning tests such as 'Rover' (0.11), 'Block counting' (0.19), and 'Pattern reasoning' (0.09).

In multivariable linear regression analysis for standardized scores, children whose mothers reported alcohol consumption during pregnancy were significantly poorer for 'Atlantis' (coefficient = -0.2, p = 0.03), 'Number recall' (coefficient = -0.6, p = 0.0001), and 'Triangle' (coefficient = -0.2, p = 0.03). They scored significantly higher errors at CCT-1 (coefficient = 0.4, p = 0.002). These results were all adjusted for age, sex, schooling, stunting, father's education, mother's employment and the promotion of exclusive breastfeeding. There was no statistical association between maternal alcohol consumption during pregnancy and neuropsychological outcomes for visual ability tests ('Conceptual thinking', 'Face recognition', 'Story completion'), as for reasoning tests ('Rover', 'Block counting', and 'Pattern Reasoning'). The strength of the association was weaker after adjusting for covariates.

3.3. Paper 2: Association between stunting and neuropsychological outcomes among children in Burkina Faso, West Africa

In paper 2, we reported the association between stunting and neuropsychological outcomes among children in Burkina Faso.

We found that stunted children did significantly less well for memory tests ('Atlantis' and 'Number Recall'), spatial ability tests ('Conceptual Thinking', 'Face Recognition' and 'Triangle'), 'General cognition' and attention, with a small effect size difference compared to non-stunted children. Stunted children scored significantly higher errors for 'cognitive flexibility' and 'inhibition', with a small effect size difference compared to children who were not stunted. For memory tests, the effect size difference was small for 'Atlantis' (0.44) and 'Number recall' (0.24). For spatial ability tests, the effect size difference was small for 'Conceptual thinking' (0.29), 'Face recognition' (0.23) and 'Triangle' (0.42). It was also small for 'General cognition' (0.48), attention (0.27), 'cognitive flexibility' (0.25) and 'inhibition' (0.30). No effect size difference was found for 'Block counting' reasoning test (0.17).

In multivariable linear regression analysis for standardized scores, stunted children did significantly less well for 'Atlantis' (coefficient = -0.4, p = 0.001), 'Number recall' (coefficient = -0.3, p = 0.02), 'Conceptual thinking' (coefficient =-0.3, p = 0.01), 'Triangle' (coefficient =-0.4, p = 0.001), 'General cognition' (coefficient = -0.5, $p \leq 0.0001$), and 'attention' (coefficient = -0.2, p = 0.04) compared to non-stunted children. Stunted children scored a significantly higher number of errors for 'cognitive flexibility' - CCT-1 (coefficient = 0.2, p = 0.02) and 'inhibition' (coefficient = 0.3, p = 0.02) compared to non-stunted children. All the results were adjusted for age, schooling, sex, playing, father's education, mother employment and promotion of previous exclusive breastfeeding. There was no statistical association between stunting and neuropsychological outcomes for 'Face recognition' and 'Block counting'. The strength of the association was weaker after adjusting for covariates.

3.4. Paper 3: Effects of schooling on aspects of attention in rural Burkina Faso

In paper 3, the association between schooling and attention measures was investigated using the Test of Variables of Attention (TOVA) among children in rural Burkina Faso

We found that children who did not attend school did significantly less well for 'Response time', 'Response time variability' 'Errors of omission', 'Errors of commission' and 'D prime score', with a small to moderate effect size difference compared to children attending school. The effect size difference was small for 'Response time' (0.38), 'Errors of omission' (0.33), and 'Errors of commission' (0.32); it was moderate for 'Response time variability' (0.56), and 'D prime score' (0.51).

In bivariate linear regression analysis for unstandardized scores, children not in school did significantly less well for 'Response time' (coefficient = 49.1, $p \leq 0.0001$), 'Response time variability' (coefficient = 31.4, $p \leq 0.0001$), 'Errors of omission' (coefficient = 19.3, $p = 0.001$), 'Errors of commission' (coefficient = 5.3, $p = 0.003$) and 'D prime score' (coefficient = -0.3, $p \leq 0.0001$) compared to children attending school.

3.5. Results of all the main exposures (maternal alcohol consumption during pregnancy, stunting, schooling) on neuropsychological outcomes in a global analysis

1.5.1. Model 1: Association between the main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes with no adjustment for confounding factors

- From model 1 (Table 5) and out of the 17 neuropsychological outcomes examined, schooling was associated in total with 11 neuropsychological outcomes ('Atlantis', 'Triangle', 'Word order', 'Story completion', 'Rover', 'General cognition', 'Total Response Time', 'Total Response Time Variability', 'Total errors of omission', 'Total errors of commission' and 'D prime score'), maternal alcohol consumption during pregnancy with 07 neuropsychological outcomes ('Atlantis', 'Triangle', 'Word order', 'Number recall', General cognition, CCT-1 and Total errors of

commission), and stunting with 04 neuropsychological outcomes ('Atlantis', 'Triangle', 'General cognition' and 'Total errors of commission').

- All the 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) were significantly associated with 04 neuropsychological outcomes ('Atlantis', 'Triangle', 'General cognition' and 'Total errors of commission').
- Maternal alcohol consumption during pregnancy and schooling were significantly associated with 01 neuropsychological outcome ('Word order').
- Maternal alcohol consumption during pregnancy alone was significantly associated with 02 neuropsychological outcomes ('Number recall' and CCT-1).
- Schooling alone was significantly associated with 06 neuropsychological outcomes ('Story completion', 'Rover', 'Total Response Time', 'Total Response Time Variability', 'Total errors of omission', 'D prime score').
- All the exposures were not associated with 04 neuropsychological outcomes ('Conceptual thinking', 'Face recognition', 'Block counting', 'Pattern reasoning').
- The multiple comparison analysis showed that all the joint 3 exposures (maternal alcohol consumption during pregnancy + stunting + schooling)) were significantly associated with all the joint 17 neuropsychological outcomes.

A summary of the results is given in Table 8.

Table 5a: Model 1 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes with no adjustment for confounding factors.

	N	Mother's alcohol consumption in pregnancy		Stunting		Schooling	
		Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Atlantis	488	-0.2 (-0.5 to -0.06)	0.01	-0.3 (-0.5 to -0.07)	0.01	0.5 (0.3 to 0.6)	0.0001
Conceptual thinking	488	-0.05 (-0.3 to 0.2)	0.6	-0.2 (-0.4 to 0.02)	0.07	0.1 (-0.03 to 0.03)	0.1
Face recognition	488	-0.09 (-0.3 to 0.1)	0.4	-0.1 (-0.4 to 0.1)	0.2	0.2 (-0.001 to 0.3)	0.05
Story completion	488	-0.04 (-0.3 to 0.2)	0.6	0.05 (-0.2 to 0.3)	0.6	0.3 (0.09 to 0.4)	0.002
Number recall	488	-0.7 (-0.9 to -0.5)	0.0001	-0.1 (-0.4 to 0.09	0.2	0.1 (-0.05 to 0.3)	0.1
Rover	488	-0.1 (-0.4 to 0.06)	0.1	-0.1 (-0.4 to 0.1)	0.2	0.3 (0.1 to 0.5)	0.002
Triangle	488	-0.3 (-0.5 to -0.07)	0.009	-0.2 (-0.5 to -0.01)	0.03	0.7 (0.5 to 0.8)	0.0001
Block counting	488	-0.2 (-0.4 to 0.1)	0.06	-0.09 (-0.3 to 0.1)	0.4	0.1 (-0.02 to 0.3)	0.08
Word order	488	-0.3 (-0.5 to -0.04)	0.01	-0.1 (-0.4 to 0.08)	0.2	0.5 (0.3 to 0.6)	0.0001
Pattern reasoning	488	-0.1 (-0.3 to 0.1)	0.2	0.1 (-0.08 to 0.4)	0.1	0.06 (-0.1 to 0.2)	0.5
Cognition	488	-0.3 (-0.6 to -0.1)	0.002	-0.3 (-0.5 to -0.07)	0.01	0.5 (0.4 to 0.7)	0.0001
CCT-1	488	0.4 (0.1 to 0.6)	0.002	0.1 (-0.08 to 0.4)	0.1	-0.1 (-0.3 to 0.05)	0.1
Total response time	488	0.1 (-0.09 to 0.4)	0.2	-0.05 (-0.3 to 0.2)	0.6	-0.3 (-0.5 to -0.2)	0.0001
Total response time variability	488	0.04 (-0.1 to 0.3)	0.7	0.08 (-0.1 to 0.3)	0.4	-0.5 (-0.6 to -0.3)	0.0001
Total errors of omission	488	0.1 (-0.04 to 0.4)	0.1	0.01 (-0.2 to 0.3)	0.9	-0.3 (-0.5 to -0.1)	0.001
Total errors of commission	488	-0.2 (-0.5 to -0.04)	0.02	0.3 (0.01 to 0.5)	0.03	-0.3 (-0.4 to -0.09)	0.003
D prime score	488	-0.03 (-0.2 to 0.2)	0.7	-0.2 (-0.4 to 0.04)	0.1	0.5 (0.3 to 0.6)	0.0001

Table 5b: **Model 1 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes, with no adjustment for confounding factors (continued).**

	Mother's alcohol consumption in pregnancy	Stunting	Schooling
	p-value	p-value	p-value
Atlantis	**	**	***
Conceptual thinking			
Face recognition			*
Story completion			**
Number recall	***		
Rover			**
Triangle	**	*	***
Block counting			
Word order	**		***
Pattern reasoning			
Cognition	**	**	***
CCT-1	**		
Total response time			***
Total response time variability			***
Total errors of omission			***
Total errors of commission	*	*	**
D prime score			***

* p≤0.05; ** p≤0.01; *** p≤0.001

1.5.2. Model 2: Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes, adjusted for all confounding factors

- From model 2 (Table 6) and out of the 17 neuropsychological outcomes, schooling was associated in total with 12 neuropsychological outcomes (‘Atlantis’, ‘Conceptual thinking’, ‘Face recognition’, ‘Story completion’, ‘Rover’, ‘Triangle’, ‘Word order’, ‘General cognition’, ‘Total Response Time’, ‘Total Response Time Variability’, ‘Total errors of omission’, ‘D prime score’), and stunting with 05 neuropsychological

outcomes (‘Atlantis’, ‘Triangle’, ‘Word order’, ‘General cognition’, ‘D prime score’).

- Stunting and schooling were significantly associated with 05 neuropsychological outcomes (‘Atlantis’, ‘Triangle’, ‘Word order’, ‘General cognition’, ‘D prime score’).
- Only schooling was significantly associated with 06 neuropsychological outcomes (‘Conceptual thinking’, ‘Story completion’, ‘Rover’, ‘Total Response Time’, ‘Total Response Time Variability’, ‘Total errors of omission’).
- All the exposures were not associated with 06 neuropsychological outcomes (‘Face recognition’, ‘Number recall’, ‘Block counting’, ‘Pattern reasoning’, CCT-1, ‘Total errors of commission’).
- The multiple comparison analysis showed that all the joint 3 exposures (maternal alcohol consumption during pregnancy + stunting + schooling)) were significantly associated with all the joint 17 neuropsychological outcomes.

All the results of model 2 were adjusted for child age, sex, history of hospitalization, history of cerebral malaria, exclusive breastfeeding, underweight/thinness, punishment, plays, mother's age, mother's employment, mother's current alcohol consumption, mother's chewing tobacco, mother's depression, father's employment, father's education, polygamy, electricity in the compound and latrine in the compound.

A summary of the results is given in Table 8.

Table 6a: **Model 2 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes adjusted for all confounding factors.**

	N	Mother's alcohol consumption in pregnancy		Stunting		Schooling	
		Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Atlantis	342	-0.17 (-0.5 to 0.2)	0.4	-0.5 (-0.8 to -0.1)	0.004	0.5 (0.3 to 0.7)	0.0001
Conceptual thinking	342	0.009 (-0.4 to 0.4)	0.9	-0.3 (-0.6 to 0.02)	0.07	0.2 (0.006 to 0.4)	0.04
Face recognition	342	0.1 (-0.2 to 0.5)	0.4	-0.2 (-0.6 to 0.03)	0.1	0.2 (0.03 to 0.4)	0.02
Story completion	342	-0.01 (-0.4 to 0.3)	0.9	-0.005 (-0.3 to 0.3)	0.9	0.3 (0.05 to 0.5)	0.01
Number recall	342	-0.2 (-0.6 to 0.1)	0.1	-0.2 (-0.6 to 0.04)	0.1	0.2 (-0.01 to 0.4)	0.07
Rover	342	0.2 (-0.2 to 0.6)	0.3	-0.3 (-0.6 to 0.06)	0.1	0.3 (0.1 to 0.5)	0.003
Triangle	342	-0.0008 (-0.3 to 0.3)	0.9	-0.5 (-0.8 to -0.2)	0.003	0.7 (0.5 to 0.9)	0.0001
Block counting	342	-0.04 (-0.4 to 0.3)	0.9	-0.1 (-0.5 to 0.1)	0.4	0.2 (0.004 to 0.5)	0.04
Word order	342	-0.1 (-0.5 to 0.2)	0.4	-0.3 (-0.7 to 0.03)	0.07	0.6 (0.4 to 0.7)	0.0001
Pattern reasoning	342	0.1 (-0.2 to 0.5)	0.5	0.01 (-0.3 to 0.4)	0.9	0.1 (-0.1 to 0.3)	0.3
Cognition	342	-0.1 (-0.4 to 0.2)	0.5	-0.5 (-0.8 to -0.2)	0.001	0.6 (0.4 to 0.8)	0.0001
CCT-1	342	0.2 (-0.2 to 0.6)	0.3	-0.01 (-0.4 to 0.3)	0.9	-0.2 (-0.4 to 0.04)	0.1
Total response time	342	-0.1 (-0.4 to 0.3)	0.9	0.01 (-0.3 to 0.4)	0.9	-0.3 (-0.5 to -0.06)	0.005
Total response time variability	342	-0.01 (-0.4 to 0.4)	0.9	0.2 (-0.1 to 0.6)	0.2	-0.4 (-0.6 to -0.1)	0.001
Total errors of omission	342	0.1 (-0.3 to 0.5)	0.6	0.2 (-0.1 to 0.6)	0.2	-0.3 (-0.5 to -0.1)	0.003
Total errors of commission	342	-0.2 (-0.6 to 0.1)	0.1	0.2 (-0.1 to 0.5)	0.1	-0.2 (-0.4 to 0.01)	0.07
D prime score	342	0.08 (-0.3 to 0.4)	0.6	-0.4 (-0.7 to -0.04)	0.02	0.4 (0.2 to 0.6)	0.0001

Coefficient adjusted for child age, sex, history of hospitalization, history of cerebral malaria, exclusive breastfeeding, underweight thinness, punishment, plays, mother's age, mother's employment, mother's current alcohol consumption, mother's chewing tobacco, mother's depression, father's employment, father's education, polygamy, electricity in the compound, and latrine in the compound.

Table 6b: Model 2 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes adjusted for all confounding factors (continued).

	Mother's alcohol consumption in pregnancy	Stunting	Schooling
	p-value	p-value	p-value
Atlantis		**	***
Conceptual thinking			*
Face recognition			*
Story completion			**
Number recall			
Rover			**
Triangle		**	***
Block counting			
Word order		*	***
Pattern reasoning			
Cognition		***	***
CCT-1			
Total response time			**
Total response time variability			***
Total errors of omission			**
Total errors of commission			
D prime score		**	***

Coefficient adjusted for child age, sex, history of hospitalization, history of cerebral malaria, exclusive breastfeeding, underweight thinness, punishment, plays, mother's age, mother's employment, mother's current alcohol consumption, mother's chewing tobacco, mother's depression, father's employment, father's education, polygamy, electricity in the compound and latrine in the compound.

1.5.3. Model 3: Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes with backward elimination adjustment of confounding factors

- In model 3 (Table 7) and out the 17 neuropsychological outcomes, schooling was associated with 12 neuropsychological outcomes (‘Atlantis’, ‘Conceptual thinking’, ‘Face recognition’, ‘Story completion’, ‘Rover’, ‘Triangle’, ‘Word order’ ‘General cognition’, ‘Total Response Time’, ‘Total Response Time

Variability', 'Total errors of omission' and 'D prime score'), stunting with 04 neuropsychological outcomes ('Atlantis', 'Triangle', 'General cognition', and 'D prime score'), and maternal alcohol consumption during pregnancy with 04 neuropsychological outcomes ('Triangle', 'Word order', 'General cognition' and CCT-1).

- All 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) were significantly associated with 02 neuropsychological outcomes ('Triangle' and 'General cognition').
- Stunting and schooling were significantly associated with 02 neuropsychological outcomes ('Atlantis', 'D prime score').
- Maternal alcohol consumption during pregnancy and schooling were significantly associated with 01 neuropsychological outcome ('Word order').
- Only maternal alcohol consumption during pregnancy was significantly associated with 01 neuropsychological outcome (CCT-1).
- Only schooling was significantly associated with 06 neuropsychological outcomes ('Conceptual thinking', 'Story completion', 'Rover', 'Total Response Time', 'Total Response Time Variability', 'Total errors of omission').
- None the exposures were associated with 05 neuropsychological outcomes ('Face recognition', 'Number recall', 'Block counting', 'Pattern reasoning', 'Total errors of commission').

The adjusted factors are given in Table 7, and a summary of results in Table 8.

Table 7a: Model 3 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting, schooling) and neuropsychological outcomes with backward elimination adjustment of confounding factors.

	Atlantis (N=371)	Conceptual Thinking (N=371)	Face Recognition (N=371)	Story completion (N=371)
Mother's alcohol consumption at pregnancy				
Coefficient (95% CI)	-4.9 (-9.9 to 0.02)	-0.03 (-0.3 to 0.2)	-0.1 (-0.4 to 0.1)	-0.07 (-0.3 to 0.2)
p-value	0.05	0.8	0.3	0.5
Stunting				
Coefficient (95% CI)	-6.4 (-11.9 to -1.3)	-0.3 (-0.6 to 0.005)	-0.2 (-0.4 to 0.1)	0.1 (-0.1 to 0.4)
p-value	0.01	0.05	0.2	0.4
Schooling				
Coefficient (95% CI)	9.3 (5.5 to 13.2)	0.2 (0.02 to 0.4)	0.1 (-0.05 to 0.3)	0.3 (0.09 to 0.5)
p-value	0.0001	0.02	0.1	0.004
Child age				
Coefficient	8.7 (3.3 to 14.2)			
p-value	0.002			
Child sex				
Coefficient (95% CI)	4.4 (0.6 to 8.2)	0.2 (0.05 to 0.4)		
p-value	0.02	0.01		
Hospitalization				
Coefficient (95% CI)		-0.3 (-0.6 to -0.05)		-0.2 (-0.5 to -0.006)
p-value		0.01		0.04
Cerabral malaria				
Coefficient (95% CI)	2.7 (0.5 to 4.9)	0.1 (0.02 to 0.2)		
p-value	0.01	0.02		
Exclusive Breatsfeeding				
Coefficient (95% CI)	-4.1 (-7.9 to -0.2)	-0.3 (-0.5 to -0.1)		
p-value	0.03	0.002		
Plays				
Coefficient (95% CI)			-0.6 (-1.0 to -0.1)	
p-value			0.008	
Mother employment				
Coefficient (95% CI)			-0.5 (-0.9 to -0.09)	
p-value			0.01	
Mothers chewing tobacco				
Coefficient (95% CI)			0.7 (0.2 to 1.2)	
p-value			0.003	
Mother depression				
Coefficient (95% CI)		0.2 (0.01 to 0.4)		
p-value		0.03		
Father emplyoment				
Coefficient (95% CI)	-7.7 (-12.9 to -2.5)	-0.3 (-0.6 to -0.01)		
p-value	0.004	0.04		
Father education				
Coefficient (95% CI)			0.3 (0.1 to 0.5)	
p-value			0.003	
Polygamy				
Coefficient (95% CI)				-0.3 (-0.4 to -0.06)
p-value				0.01

Table 7b: Model 3 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting, schooling) and neuropsychological outcomes with backward elimination adjustment of confounding factors (continued).

	Number recall (N=371)	Rover (N=371)	Triangle (N=371)	Block counting (N=371)
Mother's alcohol consumption at pregnancy				
Coefficient (95% CI)	-0.3 (-0.6 to 0.05)	0.2 (-0.1 to 0.6)	-0.3 (-0.5 to -0.03)	-0.2 (-0.5 to 0.04)
p-value	0.09	0.2	0.02	0.1
Stunting				
Coefficient (95% CI)	-0.1 (-0.4 to 0.1)	-0.09 (-0.4 to 0.2)	-0.3 (-0.6 to -0.08)	-0.1 (-0.5 to 0.1)
p-value	0.3	0.5	0.01	0.3
Schooling				
Coefficient (95% CI)	0.1 (-0.03 to 0.3)	0.3 (0.07 to 0.5)	0.7 (0.5 to 0.9)	0.1 (-0.03 to 0.3)
p-value	0.1	0.009	0.0001	0.1
Child age				
Coefficient (95% CI)			0.3 (0.07 to 0.6)	
p-value			0.01	
Child sex				
Coefficient			0.3 (0.1 to 0.5)	
95% CI			0.0001	
p-value				
Exclusive Breatsfeeding	-0.2 (-0.4 to -0.04)		-0.2 (-0.4 to -0.04)	
Coefficient (95% CI)	0.01		0.01	
p-value				
Underweight				0.4 (0.04 to 0.8)
Coefficient (95% CI)				0.03
p-value				
Plays			-0.2 (-0.3 to -0.009)	
Coefficient (95% CI)			0.04	
p-value				
Mother employment	-0.7 (-1.1 to -0.3)			
Coefficient (95% CI)	0.001			
p-value				
Mother's current alcohol consumption	-0.4 (-0.8 to -0.07)	-0.5 (-0.9 to -0.1)		
Coefficient (95% CI)	0.01	0.009		
p-value				
Father emplyoment		-0.3 (-0.6 to -0.01)	-0.4 (-0.7 to -0.1)	-0.3 (-0.6 to -0.03)
Coefficient (95% CI)		0.03	0.001	0.02
p-value				
Polygamy	-0.2 (-0.4 to – 0.06)			
Coefficient (95% CI)	0.01			
p-value				

Table 7c: Model 3 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting, schooling) and neuropsychological outcomes with backward elimination adjustment of confounding factors (continued).

	Word order (N=371)	Pattern reasoning (N=371)	Cognition (N=371)	CCT-1 (N=371)
Mother's alcohol consumption at pregnancy				
Coefficient (95% CI)	-0.3 (-0.6 to -0.08)	0.2 (-0.2 to 0.6)	-0.3 (-0.5 to -0.05)	0.4 (0.1 to 0.7)
p-value	0.009	0.3	0.01	0.004
Stunting				
Coefficient (95% CI)	-0.2 (-0.5 to 0.09)	0.1 (-0.2 to 0.4)	-0.5 (-0.8 to -0.2)	-0.04 (-0.3 to 0.2)
p-value	0.1	0.4	0.001	0.7
Schooling				
Coefficient (95% CI)	0.5 (0.3 to 0.7)	0.06 (-0.1 to 0.2)	0.5 (0.3 to 0.7)	-0.1 (-0.3 to 0.07)
p-value	0.0001	0.5	0.0001	0.1
Child age				
Coefficient (95% CI)	0.4 (0.1 to 0.7)		0.5 (0.2 to 0.7)	
p-value	0.003		0.001	
Child sex				
Coefficient (95% CI)			0.2 (0.05 to 0.4)	-0.2 (-0.5 to -0.007)
p-value			0.01	0.04
Cerabral malaria				
Coefficient (95% CI)			0.1 (0.01 to 0.2)	
p-value			0.02	
Exclusive Breatsfeeding				
Coefficient (95% CI)			-0.2 (-0.4 to -0.02)	0.2 (0.01 to 0.42)
p-value			0.02	0.03
Underweight				
Coefficient (95% CI)			0.4 (0.09 to 0.8)	
p-value			0.01	
Plays				
Coefficient (95% CI)			-0.2 (-0.4 to -0.02)	
p-value			0.02	
Mother age				
Coefficient (95% CI)	0.01 (0.003 to 0.03)			
p-value	0.01			
Mother's current alcohol consumption				
Coefficient (95% CI)		-0.4 (-0.8 to -0.02)		
p-value		0.03		
Mother depression				
Coefficient (95% CI)	0.2 (0.007 to 0.4)			
p-value	0.04			
Father emplyoment				
Coefficient (95% CI)	-0.3 (-0.6 to -0.08)		-0.6 (-0.8 to -0.3)	
p-value	0.01		0.0001	
Father education				
Coefficient (95% CI)	0.2 (0.01 to 0.4)			
p-value	0.04			
Polygamy				
Coefficient (95% CI)			-0.2 (-0.4 to -0.006)	
p-value			0.04	
Latrine in compound				
Coefficient (95% CI)				-0.2 (-0.5 to -0.01)
p-value				0.04

Table 7d: Model 3 - Association between main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes with backward elimination adjustment of confounding factors (continued).

	Total response time (N=371)	Total response time variability (N=371)	Total errors of omission (N=371)	Total errors of commission (N=371)	D prime score (N=371)
Mother's alcohol consumption at pregnancy					
Coefficient (95% CI)	0.09 (-0.2 to 0.4)	-0.002 (-0.3 to 0.3)	0.2 (-0.07 to 0.5)	-0.2 (-0.5 to 0.04)	0.005 (-0.3 to 0.3)
p-value	0.4	0.9	0.1	0.09	0.9
Stunting					
Coefficient (95% CI)	-0.001 (-0.3 to 0.3)	0.2 (-0.1 to 0.4)	0.2 (-0.1 to 0.5)	0.3 (-0.002 to 0.5)	-0.3 (-0.6 to -0.04)
p-value	0.9	0.2	0.2	0.05	0.02
Schooling					
Coefficient (95% CI)	-0.3 (-0.5 to -0.09)	-0.3 (-0.5 to -0.1)	-0.3 (-0.5 to -0.1)	-0.2 (-0.4 to 0.01)	0.4 (0.1 to 0.6)
p-value	0.004	0.001	0.003	0.07	0.0001
Child age					
Coefficient (95% CI)					0.3 (0.05 to 0.6)
p-value					0.01
Child sex					
Coefficient (95% CI)	-0.2 (-0.4 to -0.02)				
p-value	0.02				
Hospitalization					
Coefficient (95% CI)		-0.3 (-0.5 to -0.06)			
p-value		0.01			
Cerabral malaria					
Coefficient (95% CI)	-0.1 (-0.2 to -0.01)				
p-value	0.02				
Punishment					
Coefficient (95% CI)	0.6 (0.1 to 1.0)				
p-value	0.01				
Mother employment					
Coefficient (95% CI)			0.5 (0.05 to 0.9)		-0.4 (-0.8 to -0.007)
p-value			0.02		0.04
Mothers chewing tobacco					
Coefficient (95% CI)				-0.5 (-1.0 to -0.03)	
p-value				0.03	
Father education					
Coefficient (95% CI)	-0.2 (-0.4 to -0.003)				
p-value	0.04				

Table 8: Summary of the outcomes associated with the exposures for the different models.

Associated neuropsychological outcomes			
Exposures	**Model 1**	**Model 2**	**Model 3**
All three	04 outcomes	00 outcome	02 outcomes
	Atlantis, Triangle, General cognition and Total errors of commission		Triangle, General cognition
Maternal	07 outcomes	00 outcome	04 outcomes
	Atlantis, Triangle, Word order, Number recall, General cognition, CCT-1 and Total errors of commission		Triangle, Word order, General cognition and CCT-1
Stunting	04 outcomes	05 outcomes	04 outcomes
	Atlantis, Triangle, General cognition and Total errors of commission	Atlantis, Triangle, General cognition, Word order, D prime score	Atlantis, Triangle, General cognition, and D prime score
Schooling	11 outcomes	11 outcomes	11 outcomes
	Atlantis, Triangle, Word order, Story completion, Rover, General cognition, Total Response Time, Total Response Time Variability, Total errors of omission, D prime score, Total errors of commission	Atlantis, Triangle, Word order, Story completion, Rover, General cognition Total Response Time, Total Response Time Variability, Total errors of omission, D prime score, Conceptual thinking	Atlantis, Triangle, Word order, Story completion, Rover, General cognition Total Response Time, Total Response Time Variability, Total errors of omission, D prime score, Conceptual thinking

4. Discussion

4.1. Main findings

4.1.1. Discussion of the papers

In the first paper, on the association between maternal alcohol consumption in pregnancy and cognitive performance, we did not find a clear answer. The paper describes an association between maternal alcohol consumption in pregnancy and poorer cognitive performance for memory ('Atlantis' and 'Number recall') and spatial ability ('Triangle') tests, as measured by the KABC-II, and for problem solving as measured by CCT-1, among children aged 6 to 8 years in rural Burkina Faso. The effect sizes were small to moderate. Studies have described an association between maternal alcohol consumption and the offspring's neuropsychological outcomes. In a recent systematic review that includes 33 relevant studies using cognitive test scores, prenatally children exposed to alcohol did worse on problem solving, visual-spatial ability and specific domains of memory, such as immediate or delayed recall memory, compared to children who were prenatally unexposed (70). Another review highlighted the fact that heavy prenatal alcohol exposure had an adverse effect on spatial abilities and reasoning (69). In the paper, we found no statistical association between maternal alcohol consumption in pregnancy and poorer cognitive performance for 'Conceptual Thinking', 'Face recognition', 'Story completion', 'Rover', 'Block counting' and 'Pattern Reasoning'. Other studies found no difference between low to moderate alcohol consumption during pregnancy and neuro-cognitive outcomes among the offspring (71–75). The conceptual framework of drivers and outcomes of alcohol consumption (Martineau F (34)) has identified the determinants, contexts and processes of the consequences of alcohol. This is related to the socio-economic and political structure, the availability, affordability, acceptability, the quantity, the frequency and population of the consumption. Our study was conducted in rural Burkina Faso where home-brewed alcohol was available, affordable and the consumption is acceptable. In fact, the cost is low compared to commercially available alcoholic beverages in many parts of Africa (127,128). The quantity and the frequency of alcohol consumption were unknown; quantifying the amount is challenging because home-brews are often consumed in containers of variable sizes (129,130). However many biological mechanisms might contribute to alcohol-induced fetal damage, particularly deficits in brain function (131) for the association that we found.

The pathways are complex and depend on the dose, timing and pattern of the exposure (132). They include the following: (1) increased oxidative stress; (2) disturbed glucose, protein, lipid and deoxyribonucleic acid metabolism; (3) impaired neurogenesis and increased cellular apoptosis, especially of neural cells; (4) endocrine effects; and (5) effects on gene expression (133). The different pathways of action suggest that the biological teratogenic effect of alcohol is probably a result of injuries caused by several different mechanisms. It is unclear to us, why, some cognitive performances were associated and why some were not; however, beside the complex biological aspects, a possible explanation is the lack of understanding of the subtests, as discussed in the sections 4.2.3 - Languages, education and culture and 4.2.4 - Reliability and validity.

In the second paper, stunting was not associated with all the neuropsychological outcomes. The paper describes an association between stunting and poorer neuropsychological outcomes for 'General cognition' (KABC-II), 'cognitive flexibility' (CCT-1), 'attention' (TOVA) and 'inhibition' (TOVA) among aged 6-8 years old children in rural Burkina Faso. The effect sizes were mainly small. Other studies have found that stunted children performed less well and have lower scores than adequately nourished children on cognitive tests (88,89,134,135). In addition, stunted children have a disadvantage regarding reasoning skills needed for their education in early grades (90). One review highlighted the fact that childhood undernutrition was associated with concurrent and longer term deficits in cognition (136). In the paper, we found no statistical association between stunting and neuropsychological outcomes for 'Face recognition', measuring visual abilities, and 'Block counting', measuring reasoning. The absence of an association between stunting and neuropsychological outcomes was also found in other studies (89,94).

The WHO conceptual framework on Childhood Stunting (Stewart C (43)) has identified the determinants, contexts of the consequences of stunting. In this framework, the short and long term consequences of stunting are related to factors such as maternal, home environment, poor quality food, inadequate practices, food and water safety and infections in the context of community and societal factors. Our study was conducted in rural Burkina Faso where we have the presence of several risk factors. Three main pathways may explain

how stunting may affect cognitive outcomes in children for the association that we found: first, a lack of nutrients can damage the brain; second, malnourished children lack the energy to play and interact with their peers, thereby affecting their learning; and third, smaller children who appear younger than their age may receive less stimulation from adult expectations than larger children (137). It is unclear to us, why no association was found for 'Face recognition' and 'Block counting' or if this is because the association does not exist; a possible explanation of the absence of association is the lack of understanding of the subtests, as discussed in the sections 4.2.3 - Languages, education and culture and 4.2.4 - Reliability and validity. However, our findings are aligned with the 2007 Lancet series on child development to use stunting as a useful indicator by which to measure poor child development (35).

The third paper described an association between schooling and attention as measured by the 'Response time', the 'Response time variability', the 'Errors of omission', the 'Errors of commission' and the 'D prime score' of the TOVA computerized neuropsychological performance test among children aged 6-8 years in rural Burkina Faso. Schooling was associated with all the attention outcomes. The effect sizes were mainly small to moderate. No multivariable regression analysis was done for the third paper; however, it was conducted in the global analysis of the thesis using all variables, and confirmed the association between schooling and attention.

The conceptual framework of determinants of student outcomes focuses on relations between the national level, school level, class level, and student level. The framework shows the influence of national, school and teacher level to student outcomes (51). Our study was conducted in rural Burkina Faso where the education at primary school level is free of charge but often infrastructure and qualified teachers are lacking. In the rural Burkina Faso context, most primary schools have three classes and few teachers. Each student has to do the same class twice as the primary school takes 6 years; teachers are trained to differentiate students who are in the first or second year. The potential pathways underlying the effects of schooling on attention measures can be divided into 3 categories: global effects, specific effects and test-taker effects. The aspect of global effects (1) on

attention abilities is the measurement intention of psychometric test, such as TOVA, and is based on instructional experience (138,139). As soon as children start school, they are required to sit still in order to make progress with learning cultural techniques (reading, writing, arithmetic). They learn to focus their concentration on relevant aspects for a certain period of time; they learn to concentrate and resist distractions as a general ability. Studies have shown that school attendance measured more finely by additional days in school have been associated with increase scores in intelligence tests (95,97,100,140–142). School exposure has also been associated with other beneficial effects on brain development (97), and yields important development benefits and improves health, earning and human capital (143,144). Investing in schooling showed highest rate of economic returns (52). The aspect of (2) specific effects is based on the constant and repeated exercise of these cultural techniques, which lead to the development of specific skills. This might also contribute to the observed performance differences between the groups and is not entirely avoidable. The aspect of (3) test-taker effects is based on the understanding of what is being demanded of them. Studies show that exposure of children in school to the process of receiving and using instructions for learning and education improves test performance by increasing the understanding of the test-taker of what is being demanded of him/her (145,146).

4.1.2. Effects of multiple factors on children's neuropsychological outcomes

The 2016 Lancet series has identified nurturing care as the main condition that promotes the development of young children across the life-course (45,53,54). This means that factors related to nurturing care affect child development. In our study, neuropsychological outcomes were affected by factors related to responsive caregiving and the child environment, such as mothers who drink alcohol during pregnancy. Beside the biological effects of alcohol on a developing embryo discussed in paper 1, alcohol consumption also has social consequences that affect nurturing care and then the developmental potential of children (147).

In the framework, children reach their developmental potential when they are well nourished and appropriately exposed to learning. Paper 2 found an association between stunting and poorer neuropsychological outcomes, and paper 3 found an association

between schooling and attention. In addition, Models 1, 2 and 3 found that schooling was associated with most of the neuropsychological outcomes. Stunting was also associated with a number of outcomes. These findings highlight the importance of learning and good nutrition in child development, which are implicit in Sustainable Development Goals (SDG) to be achieved by 2030 (148). In fact, learning and nutrition to promote child development are embedded in at least 7 SDGs: (1) Eradicate poverty; (2) End hunger and improve nutrition; (3) Ensure healthy lives; (4) Education; (5) Achieve gender equality; (10) Reduce inequality in and among countries; (16) Promote peaceful societies; and (17) Strengthen the means of implementation (149).

Putting our three factors into the same model raises the question: how are these factors interlinked and how they are interlinked with other living conditions? The first thing to notice is that maternal alcohol consumption most likely precedes stunting and both maternal alcohol consumption and stunting precedes schooling, (Figure 12). So if there is an effect of maternal alcohol consumption on neuropsychological test outcomes, is it a direct effect or is it an indirect effect mediated through stunting, or is it mediated through stunting and schooling as indicated by the different dashed arrows? Or are there both direct and indirect effects from maternal alcohol consumption on neuropsychological test outcomes? If there are indirect effects of maternal alcohol consumption on neuropsychological test outcomes and you add stunting and schooling into the regression model, then it is possible that this will attenuate the association between maternal alcohol consumption on neuropsychological test outcomes. This is one possible interpretation of the fact that some of the associations between maternal alcohol consumption and neuropsychological test outcomes are attenuated when including all three factors in the model. Therefore, it may be justified to run both types of analyses: with all the three factors and only with each main exposure and the outcome variables. In addition, it would be important to highlight that other living conditions are continuously present; these may also attenuate the associations between the factors and the neuropsychological test outcomes.

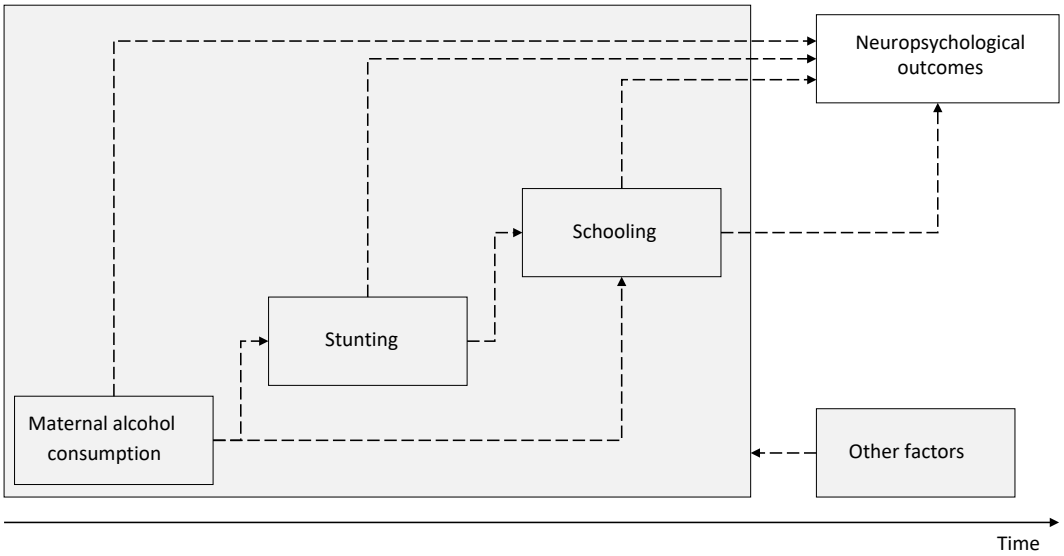

Figure 12: Interlinks between maternal alcohol consumption, stunting and schooling and other factors.

While schooling was associated with several outcomes, disadvantaged children (such as those exposed to prenatal alcohol consumption, cerebral malaria or stunting) may be less likely to attend school, and the potential of a reverse effect should not be overlooked. Comparative analysis showed that the number of children exposed to prenatal alcohol consumption (47 children not in school and 44 children in school) and not exposed to prenatal alcohol consumption (201 children not in school and 208 children in school) were similar ($p = 0.66$). Another comparative analysis showed that the number of children exposed to cerebral malaria (17 children not in school and 17 children in school), and not exposed to cerebral malaria (209 children not in school and 207 children in school), were similar ($p = 0.97$). These comparisons show that children exposed to prenatal alcohol consumption or cerebral malaria were equally likely to attend school. However for stunting, comparison showed that fewer stunted children attended school (28 children in school and 47 children out-of-school) and unstunted children had higher school attendance (217 children in school and 196 children out-of-school), $p = 0.01$. In models 1, 2 and 3, all the results have been adjusted for stunting, and yet there is a significant association between

schooling and several neuropsychological outcomes. This does not exclude reverse effects, but it strengthens our results.

Beside the association between the main exposures (maternal alcohol consumption during pregnancy, stunting and schooling) and neuropsychological outcomes, other factors related to nurturing care of the framework were considered. In fact, model 3 showed that different factors are associated with children's neuropsychological outcomes. Indeed, health-related factors (hospitalization, cerebral malaria), nutrition related factors (exclusive breastfeeding, underweight), safety and security related (punishment), and early learning related factors (plays), have been associated with neuropsychological outcomes. For (1) health-related factors, cerebral malaria is significantly associated with 04 neuropsychological outcomes ('Atlantis', 'Conceptual thinking', 'General cognition', 'Total Response Time') and hospitalization with 03 neuropsychological outcomes ('Conceptual thinking', 'Story completion', 'Total response time variability'). For (2) nutrition related factors, exclusive breastfeeding was associated with 05 outcomes ('Atlantis', 'Conceptual thinking', 'Number recall', 'Triangle', CCT-1), and underweight with 02 outcomes ('Block counting' and 'General cognition'). For (3) safety and security related factors, punishment was associated with 'Total Response Time'; and for (4) early learning-related factors, plays were associated with 03 outcomes ('Face recognition', 'Triangle' and 'General cognition'). The results compare well with existing literature, which shows that interventions and multi-factors related to nurturing care affect child development (149–152).

Factors related to caregivers, families and community were also found to be associated with child development. For instance, a father's employment was associated with 07 outcomes ('Atlantis', 'Conceptual thinking', 'Rover', 'Triangle', 'Block counting', 'Word order- and 'General cognition'); a father's education was associated with 03 outcomes ('Face recognition', 'Word order', 'Total response time'), a mother's employment with 03 outcomes ('Face recognition', 'Number recall', 'Total errors of omission'); a mother's depression with 02 outcomes ('Conceptual thinking', 'Word order'), and the presence of a latrine in the compound was associated with CCT-1.

These findings also highlight the effect of multiple factors on child development notably described by Bronfenbrenner in the ecological framework and the developmental niche framework bringing together several interconnected systems (20,21). In the transactional model, Sameroff also discussed that the development of any process in the individual is influenced by interplaying with processes in the individual's context over time (22). In the unified theory of model on development, where Sameroff integrates nature and nurture, he highlighted the importance and the influence of the environment; for instance, he discussed the necessity of the contextual model to delineate the multiple sources of experience that augment or constrain individual development, and the role of the regulation model that adds a dynamic systems perspective to the relation between a person and the context (23). The findings in this thesis are therefore consistent with these theories.

4.1.3. Notes from the field and challenges

The implementation of the study in the field had several challenges.

- The first challenge was to find conducive premises for the testing. We needed a secured and safe area with constant electricity supply because of the TOVA. On a daily basis, we were charging the computers to make sure that they were sufficiently charged; we also had inverters as a backup. In total, we conducted testing in three sites. The tables and the chairs were children sat for the testing were specially made to make sure that it was adapted to their size.
- Another challenge was that it was our first time to do psychometric testing in Burkina Faso and there was no local expertise to guide us. We had to rely on consultants and experts based out of Burkina Faso to given remote support.
- Seeing the children performing the tests, it was obvious that some of the tests such as ‘Story completion’, or ‘Pattern reasoning’ were not adapted and relevant for our rural low income country context. Thus, I am not confident on the results given by these tests. It was also interesting to see how children were fascinated by some of the tests such as TOVA.
- Explaining to the children that the testings were considered as games helped to engage with them. However, the length of the testing (almost two hours) for all the three tests was a huge challenge; in fact, even though the children were enthusiastic

and engaged at the beginning of the testing, I noticed that they were getting "bored" and "tired" at the end. Breaks between tests and ongoing engagement with the children from the beginning to the end were key. A space was available to sit, relax and play before and in-between the testings.

- Even though, the psychologists did not have previous psychometric testing experience, it was good to recruit and work with skilled professionals for the testings as they were able to understand very quickly the context and the process. The psychologists were trained on these tests for a week and conducted one month of piloting of the testing of non PROMISE SB children to be familiar with how to conduct the testing and how to engage with the children.
- After retrieving and reconsenting the children, the next challenge was the scheduling of the children for the psychometric testing. Every day, 6 children were scheduled for testing, as much as possible from the same village out of the 24 villages. As a field coordinator, I was working with two sociologists who were going to a specific planned village to schedule 6 children per working day for the following week. The children were coming to the testing site with their parent or a family member. Snacks and lunch were available and the transportation was compensated. The children were going back after the testing. For the children living far from the site, a vehicle of the health district was picking them on the scheduled day of their testing.
- The coordination between the sociologists and the parents were also challenging. On the scheduled day, some parents were not available or had forgotten about the appointment. When a scheduled child was not able to come, that child was rescheduled in the next 14 days. The children who were sick were similarly rescheduled.
- Every morning, while the sociologists were in the households to schedule testing for the following week, I had a brief group meeting with the parents and the children who were present to re-explain the context of the study. After the group session, the psychologists also had individual briefings with the parents and children before the testing. The psychologists had to verify a card which was given by the sociologists to the parents to make sure that they were part of the study. Each card had an identification code which was the first two letters of the surname and the first two

letters of the given name. For each day, I randomly allocated the children to the psychologists for the testing. It is only on the day of testing that the psychologists became aware of which children that they were going to test. The TOVA was administered first, followed by the KABC-II and the CCT1. At the end of the day before leaving, we were verifying each form to check the completeness.

- The language was a huge challenge as French was not the mother tongue of the children. Communication with the parents and children was done in one of the local languages. To be able to do this, we had to write and print the instructions in the local language. As some of the psychologists had oral but not written understanding of the language, i.e. they could speak but not read the local language, it was challenging to get them standardized. In the pilot-month before the testing started on actual PROMISE SB children they were practicing the instructions and the pronunciations of the words to be standardized.
- All the tests were conducted on the same day; and we noticed that some children were getting tired during the administration of the tests.
- Working in rural areas where even getting water is difficult (Figure 7) was also a challenge, mainly for the team. The team itself had to adapt and work in these areas.

4.2. Methodological considerations

4.2.1. Design

One strength of the thesis has been the use of children previously part of a community-based cluster-randomized trial and followed as a cohort. Concerning the design, the 3 articles are based on cross-sectional studies. Using a cross-sectional approach has disadvantages compared to a prospective study. The challenges include recall and short period of record, which is a cause of less representativeness of data. A cross-sectional design provides a “one time picture” of the reality, which is not the way in drawing causal conclusions.

Even though a cross-sectional design had some limitations, it is still sufficient to answer our questions. Furthermore, the promotion of exclusive breastfeeding by peer-counsellors that

was the main exposure variable of the previous study was retrieved and used as a confounder.

4.2.2. Internal validity

When conducting a study and making conclusions, the fundamental question is whether the study measures (or has measured) the true value. To this extent, some threats like sample size, information bias, selection bias and confounding factors should be assessed (153,154). A bias is defined as "*any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth*" (155). We will discuss next how to ensure the internal validity of the present study.

4.2.2.1. Sample size

To ensure that a true association is found when conducting a study, sufficient power is crucial to avoid type II error (156). The power is a probability of getting a set of statistical results based on the sample size (157); a type II error is committed when you conclude than there is no association, whereas in reality there is an association (157). For the 3 papers, sample size was not calculated prior to the study as the participants were recruited from a fixed sample of a community-based cohort of children. However, for the community-based cluster-randomized exclusive breastfeeding trial, the sample size was calculated to detect an increase of EBF from 20 to 40%, with a power of 80% and a confidence interval of 95% using cluster randomization (108). In total, 794 mother-infant pairs (392 in the intervention arm and 402 in the control arm) were enrolled.

In the follow-up study and the current thesis, all the children who were still alive and living in the study area were re-enrolled. For paper 1, the sample size was 518, with 96 children exposed to maternal alcohol consumption and 422 unexposed to maternal alcohol consumption. For paper 2, the sample size was 532, with 83 children exposed to stunting and 449 unexposed to stunting. And for paper 3, the sample size was 534, with 263 children attending school and 271 children not attending school. The sample size from each paper and each group (exposed or unexposed from each paper) was above 70, which is the minimal required sample size required for stable means and standard deviations in

psychological assessment (158). This indicates that the sample size may be appropriate in giving reasonable precision for the estimation of the associations. However, this interpretation should be taken cautiously as non-significant results were found in this thesis. Considering the presence of other risk factors, a more robust sample size may have showed significant results.

4.2.2.2. Information bias assessment

Information bias is a systematic error that occurs either in the way information (exposure/outcome) is collected or in the way participants provided or recalled this information. It is related to investigators and data collectors, the instruments and the study participants (159).

Information bias leads to differential and non-differential misclassification; differential misclassification is related to the value of exposure or outcome variables, and results in a "true" distortion of the association, which is measured in either direction toward the null or away from the null. In non-differential misclassification, this is the same across the groups being compared, and is related to the risk that tends to reduce the strength of the measured association (154).

In this thesis, information biases have been controlled in several ways:

1. Prior to the study, the investigators recruited data collectors, psychologists and paediatricians who understood the local languages of the study sites, and had experienced in working in rural areas where children do not have access to technology, such as computers, mobile phones or the internet. After recruitment, they were trained by experienced professionals on the study protocol, instruments and assessment tools to standardize the way to collect data and administer neuropsychological testing. In addition, a piloting of all the questionnaires and tests was conducted on local children who were not part of the study to calibrate the assessment and standardise the data collection. During implementation, the psychologists were blinded to the main exposures. All the results including insignificant findings were also presented after the analysis.

2. All the questionnaires were developed by experienced researchers and some participated in the previous community-based cluster-randomized exclusive breastfeeding trial. The questionnaires were written in a simple way to facilitate administration. To ensure the understanding of the items by the participants, the questionnaires were translated into *Dioula,* which is the main local language and back translated into French. A translation and validation workshop was conducted in presence of a specialized *Dioula* translator and all team members to ensure the accuracy of the questionnaire and its translations. The questionnaires were piloted in the field prior to their administration.

   Information about maternal alcohol consumption during pregnancy was retrospectively collected in a household interview with the caretaker prior to the neurocognitive assessment. Data collectors approached each child's household to administer a questionnaire to the child's caregiver during a one-to-one interview. Mothers were the primary respondents. A yes/no answer regarding any alcohol consumption during pregnancy was asked.

   Information on anthropometric variables (weight, height and age) were measured by a trained person at the study site prior to the neuropsychological testing and according to standard procedures (124). The stadiometer was calibrated and the height for age categories was classify according to WHO anthro (8).

   Information about schooling (child attends school - yes/no?) and the other covariates were collected in a household interview with the caretaker in the same week and prior of neurocognitive assessment. Data collectors approached each child's household to administer a questionnaire to the child's caregiver during a one-to-one interview. Mothers were the primary respondents, and responses were verified at the school.

For the outcome measures, the neuropsychological tests were selected based on the following characteristics:
(1) Tests that had previously been used in diverse cultural contexts, including Africa; this was the case for KABC-II,
(2) Tests that are fast and easy to administer in a non-verbal context; this was the case for CCT-1,
(3) Tests that are easy to administer in both population-based and clinical-based setting; this was the case for TOVA.

The neuropsychological tests were administered in a standardized way by a team of 4 trained psychologists who spoke the local languages. The instructions were translated into the main local language (*Dioula*) in the study area. Independent back-translations were completed prior to administration to check clarity. The children were randomly assigned to the psychologists for assessment. In the procedure of administration, TOVA was the first test to be used, followed by KABC-II and CCT-1 during a one-to-one session.

3. Prior to re-enrolment in the study, the protocol of the study was explained to the participants' caretakers, and written informed consent was obtained from all of them. Oral assent was also obtained from the children.

However, some information biases may have distorted the findings.

In paper 1, the assessment of alcohol consumption was retrospectively self-reported, based on a dichotomous response without further probing. Recall bias and social desirability bias must therefore be assessed. Recall bias is a *systematic error caused by differences in the accuracy or completeness of the recollections retrieved ("recalled") by study participants regarding events or experiences from the past* (155). Recall decreases in accuracy over time and seems to regress towards normal behaviour (160). Social desirability bias is *a systematic error that gives the tendency to answer question in a manner which will be favourably viewed by the others* (160).

In this study, the alcohol consumption assessment was dichotomous, with no information about the volume, frequency and concentration of alcohol consumed. Therefore, non-differential misclassification of maternal alcohol consumption with an underestimation of the association between maternal alcohol consumption and neuropsychological outcomes cannot be excluded. Other studies have shown that questions regarding alcohol consumption have usually underestimated consumption due to both recall bias and social desirability bias (161,162).

Regarding the outcome measures, we used 17 neuropsychological outcomes. Conducting multiple comparisons may be a problem as the probability of concluding that there is at least one statistically significant effect is possible, when in fact there is no effect (163,164).
The Bonferroni correction suggests that *the p value for each test must be equal or less to alpha divided by the number of tests* (165,166). In our study, when considering a Bonferroni correction with a level of significance of $\alpha=0.05/17=0.0029$ to adjust the p-values of the association between all 3 exposures (maternal alcohol consumption during pregnancy, stunting and schooling) on 17 neuropsychological outcomes, we still found statistically significant associations.

- In model 1, when considering the Bonferroni correction, schooling was associated with 10 neuropsychological outcomes ('Atlantis', 'Triangle', 'Word order', 'Story completion', 'Rover', 'General cognition', 'Total Response Time', 'Total Response Time Variability', 'Total errors of omission' and 'D prime score'), maternal alcohol consumption during pregnancy with 03 neuropsychological outcomes ('Number recall', General cognition, CCT-1 and Total errors of commission) and stunting with 00 neuropsychological outcomes. In addition, the multiple comparison analysis showed that all the joint 3 exposures (maternal alcohol consumption during pregnancy + stunting + schooling)) were significantly associated with all the joint 17 neuropsychological outcomes.
- In model 2, when considering the Bonferroni correction, schooling was associated with 06 neuropsychological outcomes ('Atlantis', 'Triangle', 'Word order', 'General cognition', 'Total Response Time Variability', 'D prime score'), stunting with 02

neuropsychological outcomes ('Triangle' and 'General cognition'), and maternal alcohol consumption during pregnancy with 00 neuropsychological outcomes. In addition, the multiple comparison analysis showed that all the joint 3 exposures (maternal alcohol consumption during pregnancy + stunting + schooling)) were significantly associated with all the joint 17 neuropsychological outcomes.

- In model 3, when considering the Bonferroni correction, schooling was associated with 06 neuropsychological outcomes ('Atlantis', 'Triangle', 'Word order' 'General cognition', 'Total Response Time Variability' and 'D prime score'), stunting with 01 neuropsychological outcome ('General cognition'), and maternal alcohol consumption during pregnancy with 00 neuropsychological outcomes.

Taken together, our assessment is that the results are consistent.

4.2.2.3. Selection bias assessment

A selection bias is a *systematic error which occurs from the selection of the participants and/or factors including response or lost-to-follow-up which affect the study participation* (167,168).

In the thesis, the participants were recruited from a previous community-based cluster-randomized trial (108). This means we had a randomly selected group initially. Among the mother-infant pair enrolled in the PROMISE EBF trial in 2006, 98 deaths occurred before 1 year, 47 after 1 year, and 83 children had moved or were out of their village at the time of the assessment. The repartition of deaths was 55% in the intervention arm and 45% in the control arm.

From the previous study, the 98 children who died before 1 year, and the 130 children who died or moved out after 1 year, would have been included if they had still been alive or available. Thus, the re-enrolled cohort is likely to have been less sick than the children who had passed away. Considering that maternal alcohol consumption and stunting are risk factors of child mortality (30,38), we could speculate that, if the cohort had been intact, it would have increased the association between both maternal alcohol consumption or stunting and neuropsychological outcomes.

Regarding dropout analysis, the rate of re-inclusion, the response rate and the completion rate were good, as described in the results Section 3.1. - Characteristics of the population.

Attrition is generally understood as the loss to follow-up of a respondent; it is inevitable with time, even with the best study design and commonly leads to bias, loss of statistical power and affects generalisability (169). In our study, the attrition rate was 29.3%. This rate is within the rates of others studies (170,171). Reasons for attrition were deaths, travels and refusal to participate in the study as described in Figure 11: Study profile. However, guidelines suggest that this is an acceptable follow-up rate (170,172). In addition, there were no significant differences in a comparison of socio-demographic characteristics of participants who died or moved out and those who were still alive, making an attrition-related selection bias less likely. Thus, we speculate that the loss to follow-up did not significantly influence the findings but this cannot be entirely ruled out.

Among the 554 children who completed the KABC-II and the CCT-1, information was missing on the exposure variables; this was 36 for maternal alcohol consumption in paper 1 and 22 for stunting in paper 2. These numbers represent 6.5% (36/554) of the missing value for maternal alcohol consumption in paper 1, and 4% (22/554) for the missing value for stunting in paper 2. In paper 3, the missing value was 0% for schooling. In all the 3 papers, the missing values were non-differential and <10%. Statistical analysis is unlikely to be biased when so few values are missing (173,174). Thus, we could expect that the missing data did not significantly influence the findings.

4.2.2.4. Confounding

A confounder is a variable which *is (1) associated with the studied outcome, (2) associated with the exposure of interest (3, and not in the causal pathway* (167). In this thesis, all the potential confounders identified in the 3 papers were used in linear regression analyses and controlled in 2 different models. Linearity between the neuropsychological outcomes and the exposures was assessed by plotting the variables. The normality of the neuropsychological outcomes was assessed by plotting the variables. In model 2, the association of maternal alcohol consumption, stunting and schooling on neuropsychological

outcomes were adjusted for all the confounding factors. In model 3, a backward elimination method was used. There are 2 main flaws with the backward elimination regression; first, it underestimates the combinations of certain variables. As the elimination process removes variables in a specific order, a combination of variables is determined by that order. The final combination of the variables may not be close to reality. Second, the final model is selected from several possible models considered by the software. This can be modified in another data set because of sample variance (175). However, backward elimination analysis is widely used. In our analysis, all the factors were included in model 3 and removed progressively based on the largest p-value until terms were significant.

4.2.3. Languages, education and culture

As described in 2.1, the study area in Burkina Faso has a low literacy rate and several local languages (102,103,105). *Dioula* is the most common spoken local language (106). In our study, the instructions of the tests were translated only in *Dioula,* given the fact that we assumed that all the children were able to speak that language. However, the team recruited spoke the other languages and understood the local context; they were therefore able to interact with the children in the other languages, but no norms were used. This methodology was the same across the different groups in all 3 papers and may have created a possible lack of variance and a floor effect (176). A floor effect is considered to be present if more than 15% of respondents were given the lowest possible score (176). Analysis of the floor effect showed that respondents achieved the lowest possible score for 'Conceptual thinking' (1.4%), 'Face recognition' (2.2%), 'Story completion' (3.2%), 'Block counting' (10.8%), 'Pattern reasoning' (15.6%) and 'Total errors of commission' (0.2%). This shows that only Pattern reasoning had a total respondent that achieved >15% of the lowest possible score. In our data, no ceiling effect was present. However, a floor effect was present for only 'Pattern reasoning'; the mixed languages and the cultural context may have distorted the tests administration and understanding. In tests that were developed and standardized in a setting, culture and language cannot be considered as valid in a setting different from the original population (55,177–179). A potential effect of cultural inappropriateness decreasing performance has been described in several studies (177,180). While cognitive constructs

appear to be universal (181), cultural context influences the engagement of the test taker in the testing process, and thus potentially the reliability and validity of the tests (180).

4.2.4. Reliability and validity

Regarding reliability, we did not assess inter-rater reliability and test-retest reliability. However, our results indicated different levels of internal consistency reliability for the subtests of the KABC-II. Malda found similar results in India (59). The internal consistency coefficient was good for 'Atlantis' (0.96), 'Conceptual thinking' (0.80), 'Face recognition' (0.74), 'Number recall' (0.76), 'Triangle' (0.78) and 'Block counting' (0.73) and CCT-1 (0.82). For TOVA, the data indicated moderate (r ranges from 0.5 to 0.79) to high internal consistency ($r \geq 0.8$) between quarters, halves and with the entire test with a slightly higher correlation coefficient in half2 (H2); this was highly comparable to the data reported in the TOVA manual (63). The internal consistency coefficient on H2 was slightly higher relative to the internal consistency coefficient on H1. This might be explained by the practice effects obtained from completing the first half, as found in other studies (182,183). The internal consistency coefficient was unsatisfactory for KABC-II 'Story completion' (0.44), 'Rover' (0.45), 'Word order' (0.64) and 'Pattern reasoning' (0.56). The low internal consistency coefficient of the subtests might be explained by the unfamiliarity of the items for the children in the cultural context. For example, regarding 'Story completion', pictures shown to the children to tell a story were not specific to their context. For 'Word order', the series of silhouettes were not common objects in the context of these children. For 'Rover' and 'Pattern reasoning', the children were unfamiliar with the type of count, game or logical figures. This has been discussed in Section 4.2.3 - Languages, education and culture. Thus, major adaptations for these tests may be needed before their use in a similar context (184). The benefits of adapting the content to improve the reliability and the validity of tests have been documented. For example, in a study in Kenya using the KABC-I, adaptations improved the validity and the reliability of the measures; 'Face recognition' was adapted by substituting the photographs with those of persons from their region for the original faces. For 'Number recall', they excluded words in local languages that had longer syllables than their English equivalents. For 'Word order', the words were appropriate, but some of the pictures were replaced by more familiar examples. For 'Triangle', the rubber triangles that

were difficult to manipulate were replaced by wooden sticks (184). A valid neuropsychological assessment of children in low income countries requires careful adaptation of materials, test items, instructions and procedures to the target setting, culture and language (55). A summary of the different tests along, with their internal consistency and suggestions for adaptations and use, are set out in Table 9.

Concurrent validity requires a gold standard and validating a neuropsychological testing especially in low income countries, where there is no gold standard, is difficult (55,185). An alternative is to validate the tool through convergent validity, which is the validity against factors known from the literature to influence neuropsychological outcomes (55,185). In this thesis, we did not have any gold standard, but the association found between factors including maternal alcohol consumption, stunting and schooling and neuropsychological outcomes support the convergent validity of KABC-II, CCT-1 and TOVA in this setting. We also did not verify the construct validity of the instruments. However, the construct validity of the KABC-II has been verified in several countries in Africa, more specifically in Benin, which is a francophone West African country like Burkina Faso (186). Therefore, we are confident that the instruments could be used in our setting and similar settings, except for 'Story completion', 'Rover', 'Word order', 'Pattern reasoning', as these subtests showed low internal consistency and need major adaptation. A recent article looking at tools for assessing early child development (0-3 years) concluded that although multiple tools exist, few are designed for multidomain child development measurement, and feasible in terms of accessibility, training requirements, clinical relevance and geography; in addition, few tools are valid and reliable in low income countries (187). A similar study of tools for this age group, 6-8 years, would most likely reach the same conclusions.

Table 9: Summary of tests internal consistencies, suggestions for adaptation and use.

Tests	Sub-tests	Internal consistency coefficient	Major adaptations needed	Current suggestion for use
CCT-1	CCT-1 errors	Good	No	Yes
TOVA	Response time	Good	No	Yes
	Response time variability	Good	No	Yes
	Errors of omission	Good	No	Yes
	Errors of commission	Good	No	Yes
	D prime score	Good	No	Yes
	Atlantis	Good	No	Yes
	Conceptual thinking	Good	No	Yes
	Face recognition	Good	No	Yes
	Number recall	Good	No	Yes
	Triangle	Good	No	Yes
KABC-II	Block counting	Good	No	Yes
	Story completion	Not Good	Yes	No
	Rover	Not Good	Yes	No
	Word order	Not Good	Yes	No
	Pattern reasoning	Not Good	Yes	No

4.2.5. Causation

Criteria to assess whether an exposure causes an outcome have been described; they include (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experiment, and (9) analogy (188). In this thesis, several criteria, including temporality, the biological gradient, and the experiment, could not be evaluated based on the study design. Thus, even though we found associations between the exposures and the outcomes, we cannot conclude any direct causation.

However, while it is difficult to conduct experimental studies on the effect of maternal alcohol consumption during pregnancy, stunting or schooling on the offspring on humans for ethical reasons, several animal studies have suggested that prenatal alcohol exposure has an effect on the development of their offspring (189). Animal studies also suggest that lack of nutrition has an effect on memory (190,191). Experimental studies on human subjects

could have been to design a study evaluating the effect of interventions to promote responsive caregiving by reducing maternal alcohol consumption, good nutrition or learning on different neuropsychological outcomes.

4.2.6. External validity – Generalization of the findings

This thesis is based on a study that was implemented in a health region in rural Burkina Faso. The participants enrolled in the PROMISE SB study from the preceding PROMISE EBF trial were generally similar to those not enrolled, due to death or migration. In addition, the participants not enrolled in PROMISE SB in Uganda and Burkina Faso were generally similar across arms with respect to gender and socio-economic parameters at inclusion (65). The generalization refers to the applicability of findings from a study population to other populations (192). In this study, the questions regarding generalization are whether the effect of exposures to maternal alcohol consumption, stunting and schooling on neuropsychological outcomes could be the same to those from similar rural context and settings.

The situation of the exposures described in this thesis has also been described in similar contexts, which include home-brewing consumption of alcohol during pregnancy (67,68), stunting (40,42) and schooling (50). This implies that the results are likely to be generalized to similar contexts.

4.2.7. Neutrality

In term of neutrality, the results presented in this thesis have several strengths.

1. The PROMISE Saving Brains study was supported by Grand Challenges Canada (grant number: #0064-03). Grand Challenges Canada is funded by the Government of Canada, and is dedicated to supporting bold ideas with big impact in global health. The funders had no role in the study design, data collection and analysis, decision to publish, or in the preparation of the results.
2. The study was presented and approved by the Institutional Review Board of Centre MURAZ number 008-2013/CE-CM.
3. The researchers involved in the study have long experience in conducting research in low income countries and there were no conflict interest. Some of them were

involved in the previous EBF trial, and knew the context and the setting. The peer-counsellors who were previously part of the EBF trial were present, and helped the retrieved children.

4. To make sure that the reporting was appropriate, all the 3 papers considered the guidelines of the "*Strengthening the Reporting of Observational Studies in Epidemiology* - STROBE" (193).

4.3. Future perspectives

In terms of perspective related to policy, the country needs to:

- Develop policies and strategic plans to improve child development,
- Develop policies to increase the number of specialists and add child development trainings in professional curricula (public health, psychology, sociology, nutrition and education),
- Develop policies and strategic plans to reduce alcohol consumption in general and maternal alcohol consumption during pregnancy in particular,
- Reinforce policies and strategic plans to reduce malnutrition, promote good nutrition, especially in rural areas,
- Reinforce policies and strategic plans to improve education, especially at a young age,
- Develop policies and strategic plans to improve statistics and data related to child development and its risk factors,
- Develop policies and strategic plans to advocate for funds for activities related to interventions to promote child development and reduce its risk factors.

In terms of perspective related to research, topics include:

- Evaluation of the role of the government in the improvement of child development in Burkina Faso,
- Field evaluation of the coverage of child development facilities in Burkina Faso,
- Adaptation and validation of KABC-II, CCT-1 and TOVA in Burkina Faso,
- Development of appropriate measurements of neuropsychological outcomes in Burkina Faso,

- Dose response of maternal alcohol intake during pregnancy, using biological gestational age and pharmacological markers on neuropsychological outcomes among children,
- Evaluation of prevention strategies of maternal alcohol consumption during pregnancy in Burkina Faso,
- Pathways of malnutrition effects on neuropsychological outcomes among children,
- Type of education, play and their dose-response on neuropsychological outcomes,
- Evaluation of barriers to (high) attendance of school in Burkina Faso and opportunities for improvement,
- Effects of nurturing care interventions (phone reward, cash transfer, awards) to improve child development outcomes in rural areas of Burkina Faso,
- Effects of child development learning programmes (including online) for professionals, families and communities to improve neuropsychological outcomes.

Conclusion

Assessing neuropsychological performance among children with many risk factors is complex. This thesis may have found some significant associations between maternal alcohol consumption during pregnancy, stunting and schooling, and poorer neuropsychological performances of children aged 6-8 years but cannot conclude on any causal relations. More structured studies with prospective collection of exposure data are needed to demonstrate causal relationships. However, this thesis shows the importance and the challenges of studying neuropsychological performances in multi-risk contexts and highlights the need for continuous promotion of child development to support children to reach their developmental potential.

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I

Maternal alcohol consumption during pregnancy and child's cognitive performance at 6–8 years of age in rural Burkina Faso: an observational study

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ABSTRACT

Background. In Burkina Faso, it is not uncommon for mothers to drink alcohol, even during pregnancy. We aimed to study the association between maternal alcohol consumption during pregnancy and the child's cognitive performance using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II) and the Children's Category Test Level 1 (CCT-1) in rural Burkina Faso.

Methods. We conducted a follow-up study of a community cluster-randomised Exclusive breastfeeding trial, and re-enrolled the children in rural Burkina Faso. A total of 518 children (268 boys and 250 girls) aged 6–8 years were assessed using the KABC-II and the CCT-1. We examined the effect size difference using Cohen's d and conducted a linear regression analysis to examine the association.

Results. Self-reported alcohol consumption during pregnancy was 18.5% (96/518). Children whose mothers reported alcohol consumption during pregnancy performed significantly poorly for memory and spatial abilities tests from small effect size difference for 'Atlantis' (0.27) and 'Triangle' (0.29) to moderate effect size difference for 'Number recall' (0.72) compared to children whose mothers did not consume alcohol during pregnancy; the exposed children scored significantly higher errors with a small effect size (0.37) at problem solving (CCT-1) test compared to unexposed children. At unstandardized and standardized multivariable analysis, children whose mothers reported alcohol consumption during pregnancy performed significantly poorer for memory-'Atlantis' ($p = 0.03$) and 'Number recall' ($p = 0.0001$), and spatial ability tests-'Triangle' ($p = 0.03$); they scored significantly higher errors at problem solving CCT-1 test ($p = 0.002$); all the results were adjusted for age, sex, schooling, stunting, father's education, mother's employment and the promotion of exclusive breastfeeding.

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No statistical association was found for visual abilities-'Conceptual Thinking', 'Face recognition', 'Story completion', and reasoning tests-'Rover', 'Block counting', and 'Pattern Reasoning'.

Conclusion. Maternal alcohol consumption during pregnancy is associated with poorer cognitive performance for memory, spatial ability, and problem solving tests in the offspring in rural Burkina Faso. Futures studies needs to assess in more detail the maternal alcohol consumption patterns in Burkina Faso and possible preventive strategies.

Subjects Neuroscience, Cognitive Disorders, Epidemiology, Psychiatry and Psychology, Public Health

Keywords Maternal alcohol consumption, Cognitive test, Child development, Pregnancy, CCT-1, KABC-II, Children, Burkina Faso, Africa

INTRODUCTION

The World Health Organization (WHO) recently stated that harmful consumption of alcohol is among the top five risk factors for disease, disability and death throughout the world. It is a causal factor in several diseases and injury conditions, and intake is on the increase, especially in low income countries (*Rehm et al., 2009*; *WHO, 2014a*).

Children exposed to prenatal alcohol have cognitive, physical and behavioural deficiencies (*Popova et al., 2016b*). Many studies have shown that regular and heavy consumption of alcohol during pregnancy are associated with neuropsychological and cognitive impairments in memory, executive function, processing speed, visual and spatial abilities, attention, language and academic achievement (*Kodituwakku, Kalberg & May, 2001*; *O'Callaghan et al., 2007*; *Falgreen Eriksen et al., 2012*; *Flak et al., 2014*). Recent reviews highlighted how prenatal alcohol can be sensitive on spatial abilities, reasoning (*Mattson, Crocker & Nguyen, 2011*), and memory (*Du Plooy et al., 2016*).

However, most of the evidence comes from high-income countries (*Lewis et al., 2015*; *Lewis et al., 2016*; *Fan et al., 2016*), and data are scarce in an African context where lack of resources, rural areas and home brewing alcohol consumption are common (*Martinez et al., 2011*). Burkina Faso is a country in Africa where the use of alcohol is increasing among women; it has among the highest national proportion of women consuming alcohol in the continent, 30% (*Martinez et al., 2011*). In 2016, a systematic review highlighted that the predicted prevalence of any amount of alcohol consumption during pregnancy among the general population in Burkina Faso was 11.3% (*Popova et al., 2016a*). According to the WHO, the level of total alcohol consumption was 6.8 litres of pure alcohol per capita for adults above 15 years of age from 2008 to 2010 (*WHO, 2014b*). The home brewed alcohol represented 84% of the type of alcohol consumed, followed by beer (10%), spirit (3%) and wine (3%) (*WHO, 2014b*).

Given the known harm from prenatal alcohol consumption and the evolving evidence of increasing drinking patterns among women in Africa, there is a need to explore alcohol consumption among pregnant women and its effect on the neuro-cognitive outcomes in their offspring in a context where lack of resources, rural areas and home brewing

alcohol consumption are common. We aimed to study the association between maternal alcohol consumption during pregnancy and the offspring's cognitive performance using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II) and the Children's Category Test Level 1 (CCT-1) in rural Burkina Faso.

SUBJECTS AND METHODS

Study area, setting, study design and participants

Burkina Faso is a low income country located in the middle of West Africa; the population resides mainly in rural areas (70.1% in 2015), and the population aged 0–14 years was 46.3% in 2013 (*INSD, 2016*; *UN Statistics, 2016*). The literacy rate is very low and the mean years of education attained in women and girls was less than 3 years in 2013 (*Patton et al., 2016*). The official language in Burkina Faso is French. However, the country has more than 60 different ethnic groups. Several local languages are spoken in the study area Gouin, Karaboro, Dioula, Senoufo, Turka, Moore, and Fulfulde (*Hama Diallo et al., 2012*; *Rossier et al., 2013*; *Ethnologue, 2016*), which is a challenge when performing cognitive testing.

In 2006, a community-based cluster-randomised trial of children was conducted, the PROMISE Exclusive Breastfeeding (EBF) study. One of the sites was in rural Burkina Faso (*Diallo et al., 2010*; *Diallo et al., 2011*; *Tylleskär et al., 2011*; *Hama Diallo et al., 2012*). The sampling has been described (*Diallo et al., 2010*; *Tylleskär et al., 2011*). From 2013 to 2015, a cross-sectional follow-up study was conducted through the PROMISE Saving Brains study to assess the neuro-cognitive performance of the children aged 6–8 years old. We sought to re-enrol all children from the initial PROMISE EBF trial who were found to be alive and still residing in the study area.

Outcome measures

The Kaufman Assessment Battery for Children, 2nd edition (KABC^{TM}-II) is an individually administered cognitive test with verbal and nonverbal components which has been used across diverse cultural contexts (*Boivin et al., 1996*; *Ochieng, 2003*; *Kaufman & Kaufman, 2004*; *Malda et al., 2010*). In Africa, it has been used to study cognitive development and nutrition in Ethiopia (*Bogale et al., 2013*), Democratic Republic of Congo (*Boivin et al., 2013*; *Bumoko et al., 2015*) and South Africa (*Taljaard et al., 2013*; *Rochat et al., 2016*), among HIV infected children in Uganda (*Boivin et al., 2010*; *Ruel et al., 2012*; *Brahmbhatt et al., 2017*), and cerebral malaria in Senegal (*Boivin, 2002*), and Uganda (*Bangirana et al., 2009*). KABC-II has different sub-tests and is used in children aged 3–18 years. The sub-tests (Appendix A) used in our study were:

- Atlantis: a measure of memory
- Conceptual Thinking: a measure of visual and spatial abilities
- Face recognition: a measure of visual and spatial abilities
- Story Completion: a measure of pattern recognition and reasoning
- Number Recall: a measure of memory
- Rover: a measure of spatial scanning and reasoning
- Triangle: a measure of spatial abilities and visualization

- Block Counting: a measure of reasoning
- Word Order: a measure of memory
- Pattern reasoning: a measure of reasoning and visualization (*Kaufman & Kaufman, 2004*; *Bangirana et al., 2009*).

The Children's Category Test Level 1 (CCT-1) is a widely used non-verbal test developed to evaluate problem solving in children; it is fast and easy to administer (*Boll, 1993*; *Hundal & Morris, 2011*; *Goudis, 2014*). It was used to examine the effect of different exposures including health conditions like traumatic injuries (*Moore, Donders & Thompson, 2004*; *Donders & Nesbit-Greene, 2004*; *Horneman & Emanuelson, 2009*), brain dysfunction (*Allen, Knatz & Mayfield, 2006*; *Bello, Allen & Mayfield, 2008*), diseases (*Rosenberg et al., 2010*), marihuana and cocaine (*Fried, Watkinson & Gray, 2005*; *Ga et al., 2015*), disabilities (*Hinton et al., 2004*), chemical products (*Debes et al., 2006*; *Wright et al., 2006*; *Jurewicz, Polańska & Hanke, 2013*), and alcohol (*Mattson et al., 1998*). CCT-1 is an individually administered standardized test for children from 5 to 8 years to test their ability to solve problems on the basis of corrective feedback. It is presented in booklet form and consists of five subtests. At the end of the test, the total number of errors is counted. Children with more errors are the one who performed worst (*Boll, 1993*; *Moore, Donders & Thompson, 2004*; *Allen, Knatz & Mayfield, 2006*).

The KABC-II and the CCT-1 were administered by a team of four trained psychologists who spoke the local languages. The children were randomly assigned to the psychologists for assessment. The assessors administered individually the KABC-II and the CCT-1 during a one-to-one session. The instructions of the measures were translated in the main local language (Dioula) commonly spoken in the study area. Independent back translations were done.

Exposure measure

Maternal alcohol consumption during pregnancy was the main exposure for this analysis. Information about maternal alcohol consumption during pregnancy was collected in a household interview with the caretaker prior to the neuro-cognitive assessment. Data collectors approached each child's household to administer a questionnaire to the child's caregiver during a one-to-one interview. Mothers were the primary respondents. A yes/no question of any alcohol consumption during pregnancy was asked. Of all the 554 caretakers, 518 were able to provide information on this question and 36 (6.5%) were not.

Covariates

In the interview, questions were asked about background characteristics and socio-economic status that may influence the child's performance. These include the child's age, child's schooling, father's employment, father's education (dichotomized to educated = at least one year in school, or not educated), mother's age, mothers' employment, mother's education, current maternal alcohol status (a yes/no question of any current alcohol consumption), mother's depression status using the Hopkins symptom checklist (*Sirpal et al., 2016*) (dichotomized to depression = at least one symptom in the checklist, no depression = no symptom in any of the checklist), mother's chewing tobacco status

(a yes/no question of current tobacco chewing), and presence of latrine in the compound (a yes/no question). Questions regarding past hospitalizations since birth of the child were asked and anthropometric data (height, age) were measured according to standard procedures (*CDC, 2007*) by a paediatrician at the study site. Stunting was defined as below-2 standard deviations of height-for-age.

Before the starting of data collection, field-testing and piloting of all the instruments was conducted to calibrate and standardize the assessment of cognitive measures and the data collection. For instance, the stadiometer for height was calibrated according to the instruction of manual, and the psychologists underwent field training and refresher training to standardize the way to administer the KABC-II and CCT-1 on local children prior to the study participants.

Statistical analysis

Statistical analyses were conducted in several stages:

1. To examine within population variance of the sub-tests, the distribution of scores (mean, standard deviation, median, minimum and maximum) were used. Box-and-whisker plots per exposed and unexposed groups were used to illustrate the children's performances on different sub-tests of KABC-II and CCT-1. Extreme scores were winsorized to discount the influence of outliers by replacing their values with the nearest scores within this range.
2. To examine the reliability of items of the sub-tests, split-half reliability coefficients were calculated for KABC-II (*Kaufman & Kaufman, 2004*; *Malda et al., 2010*) and Cronbach's alpha coefficient was calculated for CCT-1 (*Boll, 1993*; *Moore, Donders & Thompson, 2004*; *Allen, Knatz & Mayfield, 2006*). The level of significance of the reliability coefficient was $\geq$0.7.
3. To examine the association between maternal alcohol consumption during pregnancy and cognitive performance of KABC-II and CCT-1, effect size differences using the Cohen's d (*Sullivan & Feinn, 2012*; *Cumming, 2014*), and linear regression analysis were conducted. No validated norms of the KABC-II and the CCT-1 were available in Burkina Faso at the time of the study; we then used the raw scores instead of the scaled scores. However, all scores were standardized (Z) and analysis were conducted on both unstandardized and standardized scores. All the coefficients were adjusted for potential confounders including child's age, sex, schooling, stunting, father's employment, father's education (*Martinez et al., 2011*; *Falgreen Eriksen et al., 2012*; *Flak et al., 2014*; *Kesmodel et al., 2015*) and the promotion of exclusive breastfeeding ('intervention arm' of the initial trial). A bivariate analysis between each covariate and the outcome was conducted (Table A1). STATA 13 was used to perform the analysis.

Ethical considerations

Written informed consent was obtained from all care-takers in the study and oral assent was obtained from the children. The study was approved by the Institutional Review Board of Centre MURAZ number 008-2013/CE-CM.

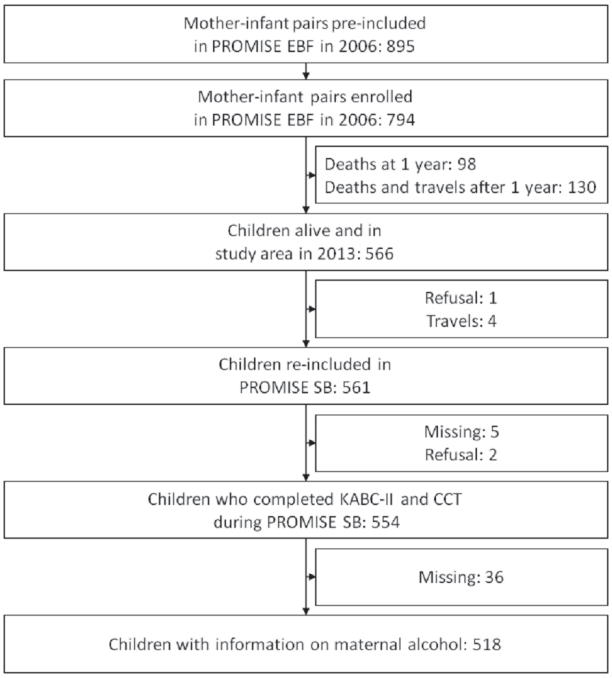

Figure 1 **Study profile of children who completed the KABC-II and having information on maternal alcohol consumption during pregnancy at the PROMISE Saving Brains study in rural Burkina Faso.**

RESULTS

Study population

Of the initial 794 enrolled children in the PROMISE EBF trial in Burkina Faso site, 561 were alive, traced and re-consented for the follow-up study, 554 children completed the KABC-II and the CCT-1, and 518 children had information on their maternal alcohol consumption status (Fig. 1).

Of these, 51.7% (268/518) were boys, and 49.4% (256/518) were at school. The mean (± standard deviation, SD) age at assessment was 7.2 (±0.4 years), the median (interquartile range, IQR) was 7.2 (6.9–7.4) years and the range was 6.3–8 years. Of the mothers, 18.5% (96/518) reported to have consumed alcohol during the pregnancy and none of them had been more than 1 year in school. The mean (±SD) age of the mothers at assessment was 33.4 (±6.3 years). Of the fathers, 30.6% (156/510) had attended at least 1 year in school and 12.9% (67/518) had an employment. Three quarters of the compounds reported having a pit latrine 73.4%, (380/518) (Table 1).

On the KABC-II, sufficient variability (mean ± SD) of the raw scores was found for all the sub-tests except 'Pattern Reasoning' (Fig. 2 and Table 2). No child scored 0 in 'Atlantis', 'Number recall', 'Rover', 'Triangle' and 'Word order' (Fig. 2 and Table 2). The Split-half

Table 1 Description of the children who completed the KABC-II and CCT-1 from the PROMISE Saving Brains study in rural Burkina Faso.

	Total *N* = 518 *N* (%)	Maternal alcohol *N* = 96 (18.5) *N* (%)	No maternal alcohol *N* = 422 (81.5) *N* (%)	*p*-value
Child age Mean ± SD (in years)	7.2 ± 0.4	7.2 ± 0.3	7.2 ± 0.4	0.38
Mothers age Mean ± SD (in years)	33.4 ± 6.3	34.4 ± 6.6	33.2 ± 6.2	0.17
Sex				0.7
Girls	250 (48.6)	45 (46.9)	205 (48.6)	
Boys	268 (51.4)	51 (53.1)	217 (51.4)	
Child in school				0.7
Yes	256 (49.4)	46 (47.9)	210 (49.8)	
No	262 (50.6)	50 (52.1)	212 (50.2)	
Stunting (<-2 SD in height-for-age)				0.8
No	426 (84.2)	79 (85.0)	347 (84.0)	
Yes	80 (15.8)	14 (15.0)	66 (16.0)	
Child has been hospitalized				0.6
No	391 (77.9)	71 (76.3)	320 (78.2)	
Yes	111 (22.1)	22 (23.7)	89 (21.8)	
Father employed				0.1
Yes	67 (12.9)	8 (8.3)	59 (14.0)	
No	451 (87.1)	88 (91.7)	363 (86.0)	
Father educated				0.8
Yes	156 (30.6)	28 (29.8)	128 (30.8)	
No	354 (69.4)	66 (70.2)	288 (69.2)	
Mother employed				0.1
Yes	26 (5.0)	2 (2.1)	24 (5.7)	
No	492 (95.0)	94 (97.9)	398 (94.3)	
Mother's current alcohol consumption				0.0001
No	89 (17.2)	25 (26.3)	19 (4.5)	
Yes	428 (82.8)	70 (73.7)	403 (95.5)	
Mothers depression status				0.2
No	267 (51.5)	55 (57.29)	212 (50.2)	
Yes	251 (48.9)	41 (42.71)	210 (49.8)	
Mothers chewing tobacco				0.0001
No	495 (95.6)	85 (88.5)	410 (97.2)	
Yes	23 (4.4)	11 (11.5)	12 (2.8)	
Latrine in compound				0.003
Yes	380 (73.4)	59 (61.5)	321 (76.1)	
No	138 (26.6)	37 (38.5)	101 (23.9)	
PROMISE EBF intervention				0.07
Control arm	274 (52.9)	43 (44.8)	231 (54.7)	
Intervention arm	244 (47.1)	53 (55.2)	191 (45.3)	

Notes.
SD, Standard deviation

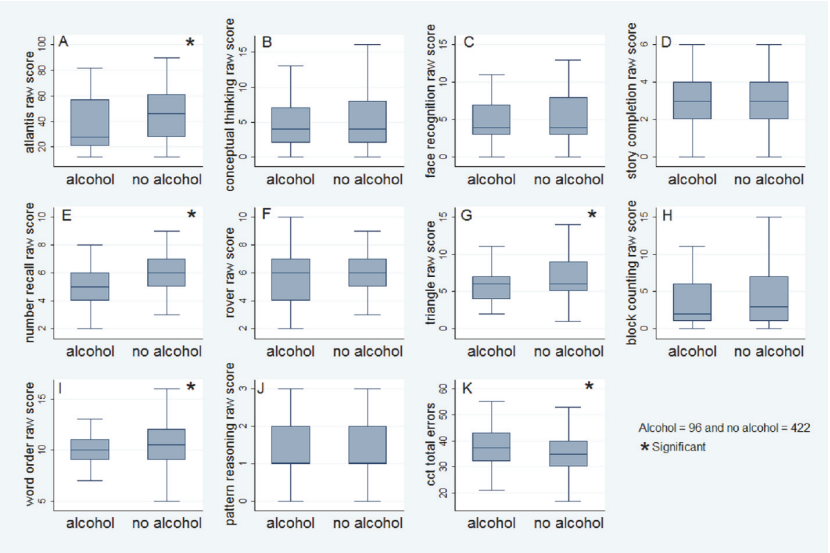

Figure 2 Box-and-whisker plots with median, interquartile range (box), minimum and maximum (whiskers) of child's performance at KABC-II subtests and CCT-1 test by maternal alcohol consumption during pregnancy from the PROMISE Saving Brains study in rural Burkina Faso. (A) Atlantis raw score; (B) Conceptual thinking raw score; (C) Face recognition raw score; (D) Story completion raw score; (E) Number recall raw score; (F) Rover raw score; (G) Triangle raw score; (H) Block counting raw score; (I) Word order raw score; (J) Pattern reasoning raw score; (K) CCT-1 total errors.

Table 2 Tests description and internal consistency of 518 children who completed the KABC-II and CCT-1 from the PROMISE Saving Brains study in rural Burkina Faso.

Tests	Mean ± SD	Median (IQR)	Min score	Max score	Reliability coefficient
Atlantis	43.5 ± 19.4	43 (28–59)	12	90	0.96
Conceptual Thinking	5.1 ± 3.4	4 (2–8)	0	16	0.80
Face recognition	5.0 ± 3.0	4 (3–8)	0	13	0.74
Story completion	3.1 ± 1.3	3 (2–4)	0	6	0.44
Number recall	5.9 ± 1.8	6 (5–7)	2	9	0.76
Rover	6.0 ± 1.9	6 (5–7)	2	10	0.45
Triangle	6.7 ± 2.8	6 (5–8)	1	14	0.78
Block counting	4.1 ± 3.6	3 (1–7)	0	15	0.73
Word order	10.4 ± 1.8	10 (9–12)	5	16	0.64
Pattern reasoning	1.5 ± 1.0	1 (1–2)	0	3	0.56
CCT-1 errors	35.6 ± 7.2	35 (31–40)	17	55	0.82

Notes.
SD, Standard deviation; IQR, Inter Quartile Range.

reliability coefficient was acceptable (>0.70) for all the sub-tests except 'Story completion', 'Rover', 'Word order' and 'Pattern Reasoning' (Table 2).

Maternal alcohol consumption and cognitive performance

Children whose mothers reported alcohol consumption during pregnancy performed significantly poorly for memory and spatial abilities tests from small effect size difference for 'Atlantis' (0.27) and 'Triangle' (0.29) to moderate effect size difference for 'Number recall' (0.72) compared to children whose mothers did not consume alcohol during pregnancy; the exposed children scored significantly higher errors with a small effect size (0.37) at problem solving (CCT-1) test compared to unexposed children (Table 3).

At unstandardized and standardized multivariable analysis, children whose mothers reported alcohol consumption during pregnancy performed significantly poorer for memory-'Atlantis' ($p = 0.03$) and 'Number recall' ($p = 0.0001$), and spatial ability tests-'Triangle' ($p = 0.03$); they scored significantly higher errors at problem solving CCT-1 test ($p = 0.002$); all the results were adjusted for age, sex, schooling, stunting, father's education, mother's employment and the promotion of exclusive breastfeeding (Table 4). No statistical association was found for visual abilities-'Conceptual Thinking', 'Face recognition', 'Story completion', and reasoning tests-'Rover', 'Block counting', and 'Pattern Reasoning' (Table 4).

DISCUSSION

In the present study, we observed an association between maternal alcohol consumption in pregnancy and poorer cognitive performance for memory ('Atlantis' and 'Number recall'), and spatial ability ('Triangle') tests as measured by the KABC-II and for problem solving as measured by CCT-1 among children aged 6 to 8 years in rural Burkina Faso. No statistical association was found for visual abilities ('Conceptual Thinking', 'Face recognition') and reasoning ('Story completion', 'Rover', 'Block counting', 'Pattern Reasoning').

Our study was conducted in an African rural context where home brewing is common and most commonly done by women. (*Martinez et al., 2011*; *WHO, 2014b*; *Popova et al., 2016a*). Its cost is low compared to commercially-made alcoholic beverages in many parts of Africa (*Mccall, 1996*; *Willis, 2002*) and quantifying its amount is challenging because home brews are often consumed in containers of various sizes (*Hahn et al., 2012*; *Thakarar et al., 2016*).

In its first application in rural Burkina Faso, we found variation in performances in the KABC-II and CCT-1. Children were positively engaged in carrying out the tests. Two things might explain the association between maternal alcohol consumption in pregnancy and poorer cognitive performance for 'Atlantis', 'Number recall', 'Triangle' and CCT-1. The first is the heavy home brewing consumption of alcohol during pregnancy. Numerous biological mechanisms have been suggested as contributing to alcohol-induced foetal damage, particularly deficits in brain function (*Goodlett & Horn, 2001*; *Kim et al., 2016*). The second is the good level of reliability for 'Atlantis', 'Number recall', 'Triangle' and 'Block counting' in accordance with the reliabilities reported in the KABC-II manual (*Kaufman et al., 2005*). Malda found similar results in India (*Malda et al., 2010*). These

Table 3 Effect size and bivariate analysis between maternal alcohol consumption during pregnancy, KABC-II and CCT-1 performance of children from the PROMISE Saving Brains study in rural Burkina Faso.

	Effect size	Bivariate analysis		*p*-value
	Cohen's d	Crude coefficient	95% CI	
Atlantis (memory)				
No alcohol		Reference		
Alcohol	0.27[a]	−5.45	−9.74 to −1.14	0.01
Conceptual Thinking (visual abilities)				
No alcohol		Reference		
Alcohol	0.02	−0.06	−0.82–0.69	0.86
Face recognition (visual abilities)				
No alcohol		Reference		
Alcohol	0.10	−0.28	−0.94–0.39	0.41
Story completion (reasoning)				
No alcohol		Reference		
Alcohol	0.05	−0.07	−0.3–0.2	0.62
Number recall (memory)				
No alcohol		Reference		
Alcohol	0.72[b]	−1.21	−1.59 to −0.84	<0.0001
Rover (reasoning)				
No alcohol		Reference		
Alcohol	0.11	−0.2	−0.6–0.2	0.29
Triangle (spatial abilities)				
No alcohol		Reference		
Alcohol	0.29[a]	−0.80	−1.42 to −0.18	0.01
Block counting (reasoning)				
No alcohol		Reference		
Alcohol	0.19	−0.71	−1.51–0.09	0.08
Word order (memory)				
No alcohol		Reference		
Alcohol	0.26	−0.5	−0.8 to −0.06	0.02
Pattern reasoning (reasoning)				
No alcohol		Reference		
Alcohol	0.09	−0.09	−0.3–0.1	0.42
CCT-1 errors (problem solving)				
No alcohol		Reference		
Alcohol	0.37[a]	2.7	1.1–4.3	0.001

Notes.
[a]Small effect size from 0.2 to 0.49.
[b]Moderate effect size from 0.5 to 0.79.

findings compare well some studies. In a recent systematic reviews of the literature which includes 33 relevant studies using cognitive test scores, children prenatally exposed to alcohol performed worse on problem solving, visual-spatial ability and specific domains of memory such as immediate or delayed recall memory compared to children who were prenatally unexposed (*Du Plooy et al., 2016*). Another review highlighted that heavy

Table 4 Multivariable analysis between maternal alcohol consumption during pregnancy, KABC-II and CCT-1 performance of children from the PROMISE Saving Brains study in rural Burkina Faso.

	Unstandardized coefficient[a] (95% CI)	Standardized coefficient[a] (95% CI)	*p*-value
Atlantis (memory)			
No alcohol			
Alcohol	−4.4 (−8.6 to −0.3)	−0.2 (−0.4 to −0.01)	0.03
Conceptual Thinking (visual abilities)			
No alcohol			
Alcohol	−0.03 (−0.8–0.7)	−0.007 (−0.2–0.2)	0.9
Face recognition (visual abilities)			
No alcohol			
Alcohol	−0.1 (−0.8–0.5)	−0.04 (−0.3–0.2)	0.7
Story completion (reasoning)			
No alcohol			
Alcohol	−0.01 (−0.3–0.2)	−0.01 (−0.2–0.2)	0.9
Number recall (memory)			
No alcohol			
Alcohol	−1.1 (−1.5 to −0.7)	−0.6 (−0.8 to −0.4)	0.0001
Rover (reasoning)			
No alcohol			
Alcohol	−0.2 (−0.6–0.2)	−0.1 (−0.3–0.1)	0.3
Triangle (spatial abilities)			
No alcohol			
Alcohol	−0.6 (−1.2 to −0.03)	−0.2 (−0.4 to −0.01)	0.03
Block counting (reasoning)			
No alcohol			
Alcohol	−0.6 (−1.4 to −0.2)	−0.2 (−0.4 to −0.06)	0.1
Word order (memory)			
No alcohol			
Alcohol	−0.3 (−0.7–0.04)	−0.2 (−0.4–0.03)	0.08
Pattern Reasoning (reasoning)			
No alcohol			
Alcohol	−0.1 (−0.3–0.1)	−0.1 (−0.3–0.1)	0.3
CCT-1 errors (problem solving)			
No alcohol			
Alcohol	2.6 (0.9–4.2)	0.4 (0.1–0.6)	0.002

Notes.

[a]Adjusted for age, sex, schooling, stunting, father's education, mother's employment, and EBF ($N = 498$).

prenatal alcohol exposure had adverse effect on spatial abilities (*Mattson, Crocker & Nguyen, 2011*).

In the present study, we found no statistical association between maternal alcohol consumption in pregnancy and poorer cognitive performance for 'Conceptual Thinking', 'Face recognition', 'Story completion', 'Rover', 'Block counting' and 'Pattern Reasoning'. Diverse explanations are possible as to why the children were not responsive to these tests.

The most plausible is that the amount of maternal alcohol consumption during pregnancy was not enough to be associated with visual abilities and reasoning tests. In our study, the level of alcohol was unknown and might have been very low to detect significance association. These results are similar to other studies which found no difference between low to moderate alcohol consumption during pregnancy and neuro-cognitive outcomes among children (*O'Callaghan et al., 2007*; *Alati et al., 2008*; *Kelly et al., 2012*; *Falgreen Eriksen et al., 2012*; *Kesmodel et al., 2012*). Also, the reliability coefficient was low for 'Story completion', 'Rover' and 'Pattern Reasoning' and we found cultural unfamiliarity of the items for 'Conceptual Thinking' and 'Face Recognition'. For example, 'Face Recognition' uses mainly photographs of faces from white people to which most children in rural Burkina Faso have not been exposed. In a study in rural Kenya using KABC-I, 'Face Recognition' has been adapted by substituted the photographs with those of persons from their region to increase the validity and the reliability of the measures (*Holding et al., 2004*). Given the fact that our study was implemented in similar context, such adaptations may have contributed to increase the responsiveness of children in our context. The reason of the low internal for 'Story completion', 'Rover' and 'Pattern Reasoning' might be explained by the weak understanding of the items; these tests measure reasoning and the understanding of the items might have been complex for the children due to the cultural context. The potential effect of cultural inappropriateness decreasing the performance has been described in multiple studies (*Greenfield, 1997*; *Malda & Van der Vijver, 2008*). While cognitive constructs appear to be universal (*Koziol et al., 2014*), the cultural context influences the engagement of the test taker in the testing process, and thus, potentially the reliability and validity of tests (*Malda & Van der Vijver, 2008*). Adaptations of the tests may therefore be needed to ensure the responsiveness of a test to group differences (*Holding et al., 2004*; *Alcock et al., 2008*). Thus, these sub-tests may differentiate children in our context after adaptations.

Our study has several strengths. Firstly, the risk of selection bias is small; the participants were part of a community-based cluster-randomised trial of children (*Diallo et al., 2010*; *Diallo et al., 2011*; *Tylleskär et al., 2011*; *Hama Diallo et al., 2012*). In addition, only two participants declined to be tested in the study. Secondly, the assessment was based on a standardized measure of cognition for children which has been widely used in a number of countries, also in Africa (*Boivin, 2002*; *Bangirana et al., 2009*; *Boivin et al., 2010*; *Ruel et al., 2012*; *Bogale et al., 2013*; *Taljaard et al., 2013*; *Bumoko et al., 2015*; *Rochat et al., 2016*; *Brahmbhatt et al., 2017*; *Ajayi et al., 2017*). In addition, the assessments were performed by trained psychologists who were blinded to the main exposure (maternal alcohol consumption). Thirdly, adjustment for the potential confounders was done in the analysis.

However, the study also has some limitations. The assessment of alcohol consumption was self-reported based on a dichotomous response without further probing. Therefore, we have no information about the volume, frequency and concentration of alcohol consumed. Misclassification of maternal alcohol consumption, in particular under-reporting and recall bias due to the recall time and social desirability cannot be excluded. However, the relatively high self-reported frequency of prenatal alcohol consumption might indicate that the population is naïve to health system information on the harmful effects on alcohol

consumption in pregnancy and provide answers with limited social desirability. Given the relatively high frequency of drinking one could also assume that only 'visible' drinking of a certain 'magnitude' is reported and 'sips'; 'low alcohol beverages' and 'ritual drinking' is not counted as drinking. Another limitation is the lack of overall reliability and validity of the measures which were used for the first time in the country and were not normed in the settings.

We consider this paper to be important as it demonstrates an association between maternal alcohol consumption and the poor cognitive performance among children in Burkina Faso. The study highlights the need to raise awareness of the risks of maternal alcohol consumption on the offspring's cognitive performance. Healthcare professionals may have an important role in advising the public on its potential consequences. Prevention initiatives need to be designed and advice on abstaining from drinking during pregnancy needs to be provided. Strategies of monitoring alcohol intake on women and children may be considered during antenatal and postnatal visits. The cognitive outcome measures needs to be validated in the local context and culturally adapted.

CONCLUSIONS

Maternal alcohol consumption during pregnancy is associated with poorer cognitive performance for memory, spatial ability, and problem solving tests in the offspring in rural Burkina Faso. Futures studies needs to assess in more detail the maternal alcohol consumption patterns in Burkina Faso and possible preventive strategies.

APPENDIX A

Outcome measures (*Kaufman & Kaufman, 2004*; *Kaufman et al., 2005*; *Bangirana et al., 2009*).

KABC-II is used in children aged 3–18 years. It has different sub-tests which include:

- **Atlantis**: The examiner teaches the child nonsense names for fanciful pictures of fish, plants and shells. The child demonstrates learning by pointing to each picture (out of an array of pictures) when it is named. 'Atlantis' is a measure of associative memory, and forms part of the learning ability scale;
- **Conceptual Thinking**: The child is presented a set of four or five pictures and must select the picture that does not belong with the set. It measures visual and spatial abilities and forms part of the simultaneous processing scale;
- **Face recognition**: The child looks at a photograph of either one or two faces for 5 s and then chooses the correct face (or faces) shown in a different pose from the original photograph. It measures visual and spatial abilities and forms part of the simultaneous processing scale;
- **Story Completion**: The child is shown a row of pictures that tell a story, with some of the pictures missing. The child should complete the story by selecting the missing pictures from a selection in their correct locations. 'Story completion' measures pattern recognition, reasoning and forms part of the planning ability scale;

- **Number Recall**: The child repeats a series of numbers in the same sequence the examiner said them. It measures memory span and forms part of the sequential processing scale;
- **Rover**: The child moves a toy dog to a bone on a checkerboard-like grid that contains obstacles (rocks and weeds) and tries to find path that takes the fewest moves. 'Rover' is a measure of spatial scanning, general sequential or deductive reasoning, number skills and forms part of the simultaneous processing scale;
- **Triangle**: For most items, the child assembles several identical foam triangles (blue on one side, yellow on the other) to match a picture of an abstract design. For easier items, the child assembles a set of colorful plastic shapes to match a model constructed by the examiner or shown on the easel. 'Triangle' measures spatial abilities, visualization and forms part of the simultaneous processing scale;
- **Block Counting**: The child counts the exact number of blocks in various pictures of stacks of blocks. The stacks are configured such that one of more blocks is hidden or partially hidden from view. 'Block counting' measures reasoning and forms part of the simultaneous processing scale;
- **Word Order**: The child touches a series of silhouettes of common objects in the same order as the examiner has named the objects. It measures memory span and forms part of the sequential processing scale;
- **Pattern reasoning**: The child is shown a series of stimuli that form a logical, linear pattern, with one stimulus missing. The child completes the pattern by selecting the correct stimulus from an array of 4–6 options at the bottom of the page. 'Pattern Reasoning' measures inductive reasoning, visualization and forms part of the simultaneous processing scale (*Kaufman & Kaufman, 2004*; *Kaufman et al., 2005*; *Bangirana et al., 2009*).

APPENDIX B

Table A1 **Crude coefficient from linear regression between covariates and the KABC-II test performance of children from the PROMISE Saving Brains study in rural Burkina Faso.**

	Atlantis	Conceptual Thinking	Face recognition	Story completion	Number recall	Rover	Triangle	Block counting	Word order	Pattern reasoning	CCT-1 errors
Age, *N*	518	518	518	518	518	518	518	518	518	518	518
Crude	6.1	0.5	−0.07	0.3	0.4	0.06	0.8	0.3	0.7	0.04	−0.9
95% CI	1.4–10.7	−0.3–1.3	−0.8–0.6	−0.004–0.6	−0.04–0.8	−0.4–0.5	0.1–1.4	−0.5–1.2	0.3–1.2	−0.2–0.3	−2.6 –0.8
p-value	0.01	0.2	0.8	0.05	0.08	0.7	0.02	0.4	0.001	0.7	0.3
Sex, *N*	518	518	518	518	518	518	518	518	518	518	518
Crude	2.13	0.5	0.09	−0.06	0.2	0.2	0.5	0.3	0.1	0.1	0.8
95% CI	−1.2–5.5	−0.1–1.1	−0.4–0.6	−0.3–1.7	−0.06–0.5	−0.1–0.5	0.04–1.0	−0.3–0.9	−0.1–0.5	−0.06–0.3	−0.4–2.0
p-value	0.2	0.1	0.7	0.6	0.1	0.1	0.03	0.3	0.3	0.2	0.2
Child in school, *N*	518	518	518	518	518	518	518	518	518	518	518
Crude	11.0	0.6	0.6	0.4	0.3	0.6	1.9	0.6	0.9	0.01	1.2
95% CI	7.8–14.2	0.03–1.2	0.07–1.1	0.1–0.6	0.04–0.6	0.3–0.9	1.5–2.4	0.01–1.2	0.6–1.3	−0.1–0.2	0.02–2.5
p-value	0.0001	0.03	0.02	0.001	0.02	0.0001	0.0001	0.04	0.0001	0.8	0.04
Stunting, *N*	506	506	506	506	506	506	506	506	506	506	506
Crude	8.1	0.8	0.6	0.06	0.3	0.4	1.06	0.6	0.6	−0.1	1.7
95% CI	3.5–12.7	0.1–1.7	−0.1–1.3	−0.3–0.4	−0.07–0.7	0.0006–0.9	0.4–1.7	−0.3–1.5	0.1–1.0	−0.4–0.09	0.01–3.5
p-value	0.001	0.03	0.09	0.7	0.1	0.05	0.002	0.2	0.006	0.2	0.04
Father educated, *N*	510	510	510	510	510	510	510	510	510	510	510
Crude	5.4	0.5	1.1	0.2	0.5	0.3	0.8	0.5	0.4	0.06	0.9
95% CI	1.8–9.0	−0.1–1.1	0.5–1.7	−0.08–0.4	0.1–0.8	−0.03–0.6	0.2–1.3	−0.2–1.2	0.1–0.8	−0.1–0.2	−0.3–2.3
p-value	0.004	0.1	0.0001	0.1	0.006	0.08	0.004	0.1	0.01	0.5	0.1
Mother's employment, *N*	518	518	518	518	518	518	518	518	518	518	518
Crude	5.8	0.2	1.6	0.1	1.4	0.2	0.9	1.6	0.9	0.1	3.7
95% CI	−1.8–13.4	−1.0–1.6	0.4–2.7	−0.3–0.6	0.7–2.1	−0.5–0.9	−0.1–2.0	0.2–3.0	0.1–1.6	−0.3–0.5	0.8–6.6
p-value	0.1	0.6	0.008	0.5	0.0001	0.5	0.07	0.02	0.01	0.5	0.01
PROMISE EBF intervention, *N*	518	518	518	518	518	518	518	518	518	518	518
Crude	−0.8	−0.8	−0.3	−0.1	−0.3	−0.01	−0.4	0.06	−0.006	−0.06	1.2
95% CI	−4.2–2.5	−1.4 to −0.2	−0.8–0.2	−0.3–0.07	−0.6 to −0.001	−0.3–0.3	−0.9–0.04	−0.5–0.6	−0.3–0.3	−0.2–0.1	−0.04–2.4
p-value	0.6	0.005	0.2		0.04	0.9	0.07	0.8	0.9	0.4	0.059

ADDITIONAL INFORMATION AND DECLARATIONS

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The authors declare there are no competing interests.

Author Contributions

- Anselme Simeon Sanou, Abdoulaye Hama Diallo and Penny Holding conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
- Victoria Nankabirwa conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, reviewed drafts of the paper.
- Ingunn Marie S. Engebretsen, Thorkild Tylleskar and Esperance Kashala-Abotnes conceived and designed the experiments, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
- Grace Ndeezi conceived and designed the experiments, contributed reagents/materials/-analysis tools, reviewed drafts of the paper.
- James K. Tumwine conceived and designed the experiments, contributed reagents/-materials/analysis tools, reviewed drafts of the paper, was principal investigator of the PROMISE Saving Brains study.
- Nicolas Meda conceived and designed the experiments, performed the experiments, contributed reagents/materials/analysis tools, reviewed drafts of the paper, was co-Principal investigator of the PROMISE Saving Brains study.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The study was approved by the Institutional Review Board of Centre MURAZ.

Data Availability

The following information was supplied regarding data availability:

The raw data has been uploaded as Data S1.

Supplemental Information

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Association between stunting and neuro-psychological outcomes among children in Burkina Faso, West Africa

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Abstract

Background: In Burkina Faso, stunting affects children and is a public health problem. We studied the association between stunting and child's neuro-psychological outcomes at 6–8 years of age in rural Burkina Faso using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), the Children's Category Test 1 (CCT-1) and the Test of Variable of Attention (TOVA).

Methods: We re-enrolled children of a previously community-based Exclusive breastfeeding trial in Burkina Faso. We assessed a total of 532 children aged 6–8 years using KABC-II for memory (Atlantis and Number Recall subtests), spatial abilities (Conceptual Thinking, Face Recognition and Triangle subtests), reasoning (Block Counting subtest), general cognition and CCT-1 for cognitive flexibility. A total 513 children were assessed using the TOVA to measure attention and inhibition. We calculated the Cohen's d to examine the effect size and conducted a linear regression to examine the association.

Results: The proportion of stunting was 15.6% (83/532). Stunted children performed significantly poorer for memory (Atlantis and Number Recall), spatial abilities (Conceptual Thinking, Face Recognition and Triangle), general cognition and attention with a small effect size compared to non-stunted children. Children who were exposed scored significantly higher errors for cognitive flexibility and inhibition with a small effect size compared to unexposed children. At standardized and unstandardized multivariable regression analysis, stunted children performed significantly poorer for Atlantis ($p = 0.001$), Number Recall ($p = 0.02$), Conceptual Thinking ($p = 0.01$), Triangle ($p = 0.001$), general cognition ($p \leq 0.0001$) and attention ($p = 0.04$) compared to non-stunted children. Children who were exposed scored significantly higher errors for cognitive flexibility ($p = 0.02$) and for inhibition ($p = 0.02$) compared to unexposed children. We adjusted all the results for age, schooling, sex, playing, father education, mother employment and promotion of previous exclusive breastfeeding.

Conclusion: Stunting is associated with poorer neuro-psychological outcomes among children in rural Burkina Faso. Initiatives related to prevention need to be established and advice on nutrition need to be provided.

Keywords: Stunting, Nutrition, Neuro-psychological test, KABC-II, CCT-1, TOVA, Children, Burkina Faso, Africa

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Background

Stunting affects more than 165 million children in the world and is highly prevalent from 20 to 35% in sub-Saharan Africa [1, 2]. In Burkina Faso, it is public health problem and varies from 8% for 10–12 years children [3], to 29% for 1–5 years and 8–14 years children [4, 5]. Poor nutrition among children is a major risk factor in several diseases, disabilities, delayed cognitive development in childhood, increased a longer-term risk of chronic disease, reduced income in adulthood and deaths throughout the world [2, 6–9]. It is one of the best overall indicator of children's well-being and an accurate reflection of social inequalities [10]. Stunting is closely tied to access to services, poverty and causal factors include prenatal and postnatal periods [11–13]. In sub-Saharan Africa, it has several socio-demographic and family factors [14–19].

Many studies in low-income countries have shown that stunting is associated with cognitive outcomes; in different studies, associations were found between stunting and cognitive ability at 5 years, during adolescence and at age 20–22 years [9, 20–22]. Children who experienced stunting in early childhood may have deficiencies related to cognition, school performance and intelligence deficits [23–31]. Also, risk factors of stunting including child's education, home environment and parental education were found to affect child cognition [32, 33].

More specifically, stunting is associated with verbal comprehension and performance abilities [23], language comprehension, memory [24], vocabulary [24, 27], problem solving and executive function [29], reasoning [31], general cognition [24, 25]. However, the studies showing the effect of stunting on neuro-psychological outcomes used traditional tests administered by human examiner; those tests are non computerized one-on-one tests and some of them are the Bayley mental and motor scales [34], the Weschler Intelligence Scales [35], the Ravens Progressive Matrices [36]. While much is known about poor nutrition association and cognitive outcomes using traditional tests, data from West Africa is scarce and gaps in knowledge still persist in the effect of stunting using computerized neuro-psychological testing.

Children's neuro-psychological outcomes can be assessed by a variety of neuro-psychological tests. One of the traditional human administered tests is the Kaufman Assessment Battery for Children, Second Edition (KABC-II) [37]. Another human administered test is the first level of the Children's Category Test (CCT-1) developed to assess cognitive flexibility in children [38]. Both tests were used in the country [39]. The Test of Variables of Attention (TOVA) is a used computerized neuro-psychological (Leark et al. [49]). It measures attention and has been used to explore multiple health and developmental risks in the exploration of attention and was used in Africa [40–42].

Given the gaps of knowledge of the effect of stunting on neuro-psychological outcomes using both traditional and computerized tests in general and in West Africa in particular, we studied the association between stunting and neuro-psychological outcomes using KABC-II, CCT-1 and TOVA among children in Burkina Faso.

Methods

Setting, study area, participants and study design

Burkina Faso is a West African country with 46.3% of the population aged 0–14 years, and 70.1% living mainly in rural areas [39, 43, 44]. We re-enrolled children of a previously community-based Exclusive breastfeeding trial in Burkina Faso conducted in 2006 [45]. The sampling and further details of the participants and study site was described [39, 45, 46].

Outcome measures

The KABC-II is used for children aged 3–18 years and has several subtests [37, 39, 47]. The total raw score of the subtests was used as a measure of general cognition. The KABC-II 'Atlantis' and 'Number Recall' subtests were used as measures of memory; 'Conceptual Thinking', 'Face Recognition' and 'Triangle' were used as measures of spatial abilities. 'Block Counting' was used as a measure of reasoning. The KABC-II subtests 'Atlantis', 'Number Recall', 'Conceptual Thinking', 'Face Recognition', 'Triangle' and Block Counting' were considered in the study as they showed good reliability in rural Burkina Faso [39].

The CCT-1 is a test used for children aged 5–8 years and counts the number of errors [38, 39, 48]. In our study, we used the total raw errors as a measure of cognitive flexibility.

The visual TOVA is a computerized test developed to assess attention and inhibition. In our study, we used the TOVA to measure attention and inhibition [41, 49–51]. Attention was measured by the D prime score and inhibition was measured by the error of commission. The D prime score is a response sensitivity score and is interpreted as a measure of accurate performance over time and errors of commission are inappropriate responses to the non-target stimulus [41, 49–51]. Those variables were automatically exported from TOVA on the computer.

In the procedure of administration, TOVA was the first test to be performed, followed by KABC-II and CCT-1. Further details of the administration procedures have been described [39].

Exposure measure

Stunting at 6–8 years old was the exposure measure. A paediatrician measured anthropometric variables (height, age) at the study site prior to the neuro-psychological testing and according to standard procedures [52]. We defined stunting as below −2SD of height-for-age. We calibrated the stadiometer according to the instructions of the manual. WHO Anthro was used to classify the children into height for age categories of nutritional status [53].

Covariates

Socio-economic status, background characteristics' and clinical history questions were asked prior to neuro-psychological assessments. These include child's age, schooling, playing with objects at home which was shown to stimulate neuro-psychological outcomes [54], child was beaten in the last 12 months, mother's age, mother's education, mother's employment, mother's depression (depressed or not depressed) using the Hopkins symptoms depression status [55], father's education, father's employment, polygamy, presence of electricity in the compound. It also included history of cerebral malaria and past hospitalizations. Anthropometric measures (weight, height, age) were collected. We defined Underweight as below −2SD of weight-for-age and thinness as below −2 SD of BMI-for-age. The promotion of exclusive breastfeeding which was the intervention of the PROMISE EBF trial was retrieved. Further details of the piloting and the field-testing of all the tools have been described [39].

Statistical analysis

The variance of the population was examined using scores' distribution (mean, standard deviation, median, minimum and maximum). Covariates' differences by stunting were tested using student test, Chi square analyses, Fisher exact test. The effect size was examined using Cohen's d calculation and the association between stunting and the neuro-psychological outcomes was conducted using linear regression. Both unstandardized scores (using raw scores of the neuro-psychological tests) and standardized z-scores (all the raw scores were converted to z-values, mean = 0, SD = 1) were used in the analysis. We adjusted the coefficients for potential confounders [30, 31] and also for the previous intervention. A bivariate analysis was conducted with the covariates (Additional file 1). The statistics tests were declared significant at the 5% level and were two-sided. The analysis was performed using STATA 13. The analysis methodology was previously used [39].

Ethical considerations

We obtained a written informed consent from all the care-takers and an oral assent from the children. The Institutional Review Board (IRB) of Centre MURAZ has approved the study number 008-2013/CE-CM.

Results

Study population

Of the 794 children enrolled in the previous PROMISE EBF trial, 561 were re-consented for the PROMISE SB follow-up study, 554 children were assessed for neuro-psychological testing, and information on stunting was collected for 532 children (Fig. 1).

Of these, 15.6% (83/532) were stunted, 52.8% (281/532) were boys, and 49.8% (265/532) were at school. Children's age was ranged from 6.3 to 8.0; the median age (IQR) of the children during assessment was 7.2 (6.9–7.4). Amongst the children, 10.2% (54/531) were underweight, 23.0% (120/522) had history of hospitalization and 47.7% (242/507) played with objects at home.

At the time of assessments, the mean (±SD) age of the mothers was 33.3 (±6.3 years). Amongst the fathers, 13.4% (68/507) had an employment. Electricity was reported in 77.3% (392/507) (Table 1). Underweight, child's sex, schooling and mother's depression status were statistically associated with stunting ($p < 0.05$) (Table 1).

The mean (±SD) of the scores of the tests was 91.6 ± 28.8 for general cognition (KABC-II), 35.6 ± 7.2 for cognitive flexibility (CCT-1), 2.3 ± 0.6 for attention (TOVA) and 27.3 ± 16.5 for inhibition (TOVA) (Fig. 2 and Table 2).

Stunting and neuro-psychological outcomes

Stunted children performed significantly poorer for memory ('Atlantis' and 'Number Recall') and spatial abilities ('Conceptual Thinking', 'Face Recognition' and 'Triangle') tests with a small (between 0.2 and 0.49) effect size difference compared to non-stunted children (Table 3). Stunted children also performed significantly poorer for general cognition (Cohen's d = 0.48) and attention measure (Cohen's d = 0.27) with small effect size compared to non-stunted children. Children who were exposed scored significantly higher errors for cognitive flexibility (Cohen's d = 0.25) and inhibition (Cohen's d = 0.30) with small effect sizes compared to unexposed (Table 3).

At standardized and unstandardized multivariable regression analysis, stunted children performed significantly poorer for memory ($p = 0.001$ for 'Atlantis' and $p = 0.02$ for 'Number Recall') and for Visual abilities ($p = 0.01$ for 'Conceptual Thinking' and $p = 0.001$ for 'Triangle') tests for age, schooling, sex, playing, father education, mother employment and promotion of previous exclusive

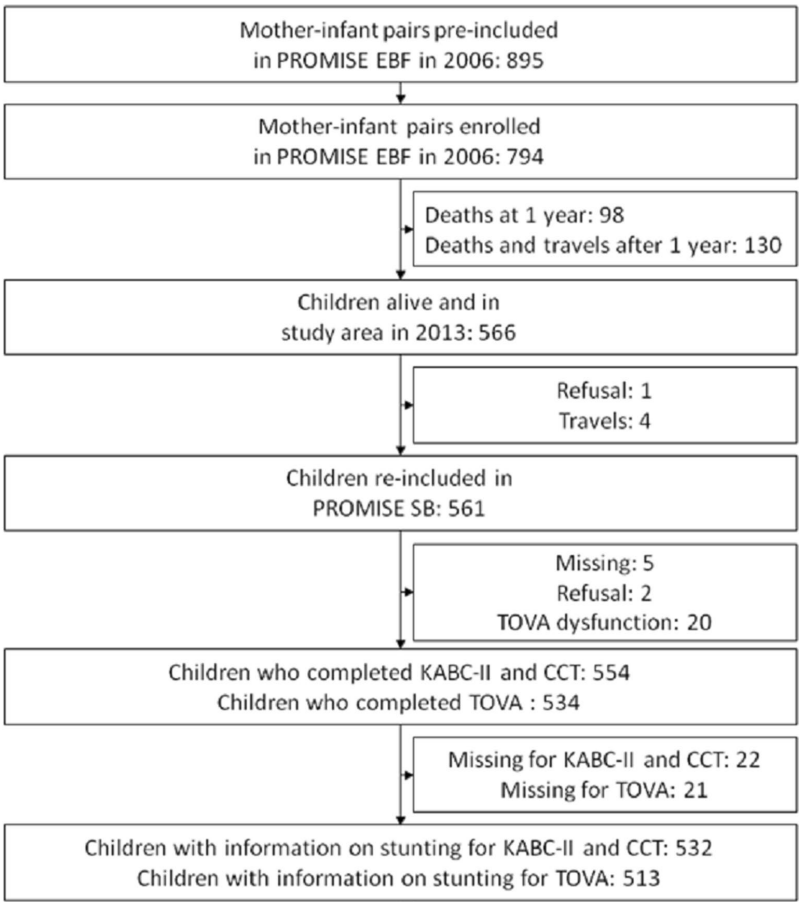

Fig. 1 Study profile of children at the PROMISE SB study in Burkina Faso

breastfeeding (Table 4). Stunted children also performed significantly poorer in general cognition ($p \leq 0.0001$) and for attention measure ($p = 0.04$) compared to non-stunted children. The children who were stunted scored significantly higher errors for cognitive flexibility ($p = 0.02$) and for inhibition ($p = 0.02$) compared to non-stunted children. We adjusted all the results for age, schooling, sex, playing, father education, mother employment and promotion of previous exclusive breastfeeding (Table 4).

Discussion

In our study, we found that stunting was associated with poorer neuro-psychological outcomes for memory ('Atlantis'—KABC-II and 'Number Recall'—KABC-II), spatial ability ('Conceptual Thinking'—KABC-II and 'Triangle'—KABC-II), general cognition (KABC-II), cognitive flexibility (CCT-1), attention (TOVA) and inhibition (TOVA) among aged 6–8 years old children in rural Burkina Faso.

The study was carried out in an African rural context where stunting is prevalent and is a public health problem. Three main pathways explain how stunting may affect cognitive outcomes in children: first, a lack of nutrients can damage the brain; second, malnourished children lack the energy to interact with their peers affecting their learning; third, smaller children who appear younger than their age may receive less stimulation from adult expectations than larger children [56].

Table 1 Description of the children who completed KABC-II CCT-1 from PROMISE SB in Burkina Faso

	Total N = 532 N (%)	No stunting N = 449 (84.40)	Stunting N = 83 (15.60)	P value
Child age mean ± SD (in years)	7.2 ± 0.4	7.2 ± 0.4	7.2 ± 0.4	0.36
Mothers age mean ± SD (in years)	33.3 ± 6.3	33.4 ± 6.4	33.1 ± 6.0	0.75
Underweight (< − 2 SD in weight-for-age)				≤ 0.0001
No	477 (89.8)	431 (96.0)	46 (56.1)	
Yes	54 (10.2)	18 (4.0)	36 (43.9)	
Thinness (< − 2 SD in BMI-for-age)				0.96
No	512 (96.4)	433 (96.4)	79 (96.3)	
Yes	19 (3.6)	16 (3.6)	3 (3.6)	
Sex				0.01
Girls	251 (47.2)	227 (50.6)	54 (65.1)	
Boys	281 (52.8)	222 (49.4)	29 (34.9)	
Child in school				0.003
Yes	265 (49.8)	236 (52.6)	29 (34.9)	
No	267 (50.2)	213 (47.4)	54 (65.1)	
Child has been hospitalized				0.57
No	402 (77.0)	340 (76.6)	62 (79.5)	
Yes	120 (23.0)	104 (23.4)	16 (20.5)	
Child has history of cerebral malaria				0.11
No	443 (91.1)	380 (92.0)	63 (86.3)	
Yes	43 (8.9)	33 (8.0)	10 (13.7)	
Child plays with object at home				0.77
No	265 (52.3)	222 (52.0)	43 (53.8)	
Yes	242 (47.7)	205 (48.0)	37 (46.2)	
Child was beaten in the last 12 months				0.06
No	483 (95.3)	410 (96.0)	73 (91.3)	
Yes	24 (4.7)	17 (4.0)	7 (8.7)	
Father employed				0.79
Yes	68 (13.4)	58 (13.6)	10 (12.5)	
No	439 (86.6)	369 (86.4)	70 (87.5)	
Father educated				0.19
Yes	153 (30.5)	124 (29.4)	29 (36.7)	
No	348 (69.5)	298 (70.6)	50 (63.3)	
Mother employed				0.11
Yes	26 (5.1)	19 (4.5)	7 (8.8)	
No	481 (94.9)	408 (95.5)	73 (91.2)	
Mothers depression status				0.04
No	263 (52.9)	230 (54.9)	33 (42.3)	
Yes	234 (47.1)	189 (45.1)	45 (57.7)	
Polygamy (father has more than 1 wife)				0.24
No	181 (35.7)	157 (36.8)	24 (30.0)	
Yes	326 (64.3)	270 (63.2)	56 (70.0)	
Electricity in compound				0.15
Yes	392 (77.3)	335 (78.5)	57 (71.3)	
No	115 (22.7)	92 (21.5)	23 (28.7)	
PROMISE EBF intervention				0.10
Control arm	284 (53.4)	233 (51.9)	51 (61.5)	
Intervention arm	248 (46.6)	216 (48.1)	32 (38.5)	

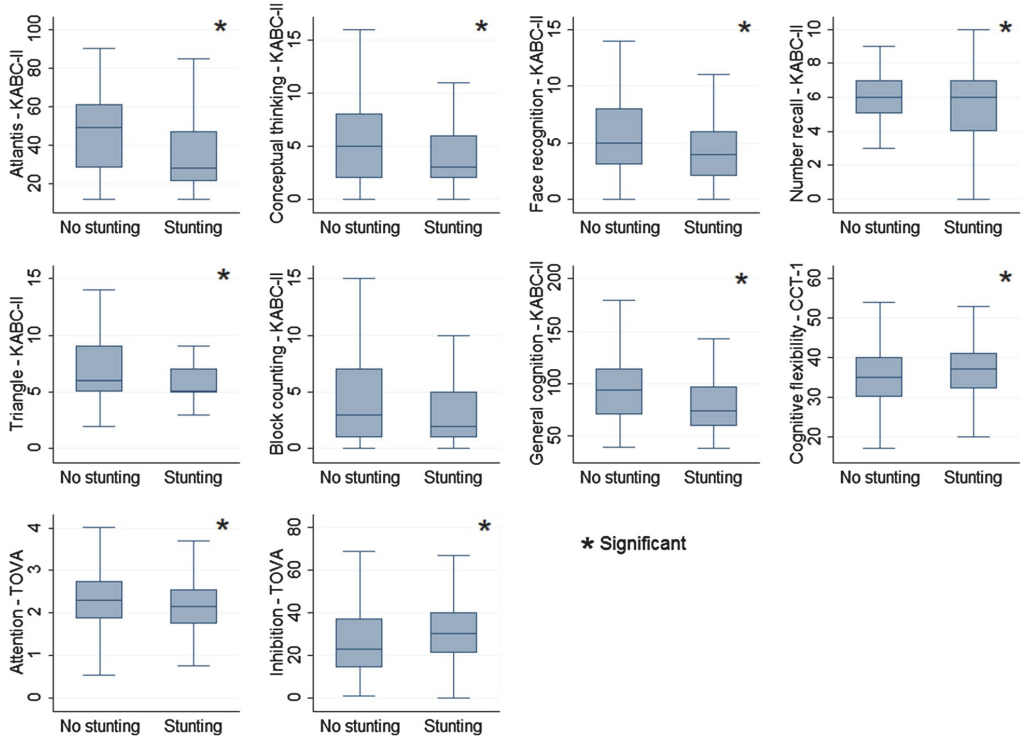

Fig. 2 Box-and-whisker plots of neuro-psychological outcomes by stunting from the PROMISE SB study in Burkina Faso

Table 2 Neuro-psychological outcomes of children from the PROMISE SB in Burkina Faso

Tests	Unstandardized raw score				Standardized z-score		
	Mean ± SD	Median (IQR)	Min	Max	Median (IQR)	Min	Max
Memory (Atlantis—KABC-II)	43.4 ± 19.3	43 (28–58)	12	90	− 0.02 (− 0.8 to 0.8)	− 1.6	2.4
Visual abilities (Conceptual Thinking —KABC-II)	5.1 ± 3.4	4 (2–8)	0	16	− 0.3 (− 0.9 to 0.8)	− 1.5	3.2
Visual abilities (Face Recognition—KABC-II)	5.0 ± 3.0	4 (3–7)	0	14	− 0.3 (− 0.6 to 0.8)	− 1.6	2.9
Memory (Number Recall—KABC-II)	6.0 ± 1.8	6 (5–7)	0	10	0.05 (− 0.5 to 0.6)	− 3.2	2.2
Spatial abilities (Triangle—KABC-II)	6.7 ± 2.8	6 (5–8)	2	14	− 0.2 (− 0.6 to 0.5)	− 1.7	2.6
Reasoning (Block Counting—KABC-II)	4.1 ± 3.6	3 (1–7)	0	15	− 0.3 (− 0.8 to 0.8)	− 1.1	3.0
General cognition (KABC-II)	91.6 ± 28.8	90 (67–113)	38	179	− 0.04 (− 0.8 to 0.7)	− 1.8	3.0
Cognitive flexibility (CCT-1)	35.6 ± 7.2	35 (31–40)	17	54	− 0.08 (− 0.6 to 0.6)	− 2.6	2.5
Attention (TOVA)	2.3 ± 0.6	2.3 (1.8–2.7)	0.5	4.0	− 0.01 (− 0.7 to 0.6)	− 2.6	2.6
Inhibition (TOVA)	27.3 ± 16.5	24 (15–37)	0	69	− 0.20 (− 0.7 to 0.5)	− 1.6	2.5

SD Standard deviation, *IQR* Inter Quartile Range

Our findings compares well with other studies which found that stunted children performed poorly and had much lower scores than adequately nourished children on cognitive tests [29, 30, 57, 58]. In addition, stunted children have a disadvantage regarding reasoning skills needed for their education in early grades [31]. A review

Table 3 Effect size and bivariate analysis using linear regression between stunting and outcome measures

	Effect size Cohen's d	Unstandardized Coefficient (95% CI)	Standardized Coefficient (95% CI)	P value
Memory (Atlantis—KABC-II)	0.44[a]	− 8.6 (− 13.1 to − 4.1)	− 0.4 (− 0.6 to − 0.2)	0.0002
Visual abilities (Conceptual Thinking—KABC-II)	0.29[a]	− 0.9 (− 1.8 to − 0.2)	− 0.2 (− 0.5 to − 0.05)	0.01
Visual abilities (Face Recognition—KABC-II)	0.23[a]	− 0.7 (− 1.4 to − 0.01)	− 0.2 (− 0.5 to − 0.002)	0.04
Memory (Number Recall—KABC-II)	0.24[a]	− 0.4 (− 0.9 to − 0.01)	− 0.2 (− 0.5 to − 0.006)	0.04
Spatial abilities (Triangle—KABC-II)	0.42[a]	− 1.2 (− 1.8 to − 0.5)	− 0.4 (− 0.6 to − 0.2)	0.0004
Reasoning (Block Counting—KABC-II)	0.17	− 0.6 (− 1.5 to 0.2)	− 0.2 (− 0.4 to 0.05)	0.1
General cognition (KABC-II)	0.48[a]	− 13.9 (− 20.5 to − 7.2)	− 0.5 (− 0.7 to − 0.2)	≤ 0.0001
Cognitive flexibility (CCT-1)	0.25[a]	1.8 (0.1 to 3.5)	0.3 (0.01 to 0.5)	0.03
Attention (TOVA)	0.27[a]	− 0.2 (− 0.3 to − 0.02)	− 0.3 (− 0.5 to − 0.03)	0.02
Inhibition (TOVA)	0.30[a]	5.0 (1.0 to 8.9)	0.3 (0.06 to 0.5)	0.01

[a] Small effect size from 0.2 to 0.49

highlighted that childhood under nutrition was associated with concurrent and longer term deficits in cognition [59].

In our results, we found several socio-demographic and family factors including sex, education, maternal depression, which were associated with stunting. These results were found in other studies [14–19]. Sex difference varies in stunting; while some studies demonstrated higher levels of stunted boys [60–62], others demonstrated higher levels of stunted girls [63, 64]. Our study found a larger percentage of stunted girls than boys. The reason could be the increased access to food due to the cultural preference of boys at birth [65, 66]. The association between higher education and low stunting could be explained by the fact that educated people are more likely to take decisions which will improve their nutrition [67]. Regarding the effect of maternal depression on stunting, it could be explained by the fact it is associated with deficient child's psychological, emotional and physical stimulation, a reduced interest in infant caring activities, and unhealthy lifestyles [68, 69]. Our results also found less stunting children in the exclusive breastfeeding group compared to the control group. This could be explained by the fact that liquids different from breast-milk increases the risk of disease, which may result in micronutrient deficiencies and growth retardation [70]. However, exclusive breastfeeding was not associated with stunting. Different studies did not find any effect of exclusive breastfeeding in growth [70–73].

There are several strengths in our study. Firstly, there is a small selection bias risk; the participants were included in a previous community-based trial [45, 74]. Secondly, height was measured according to standardized procedures and with a calibrated stadiometer. Thirdly, all the measurements were based on widely used of standardized measures of neuro-psychological outcomes for children in Africa [41, 47, 75–78]. Also, only trained blinded to stunting psychologists assessed the children [39]. Finally, we adjusted for potential confounders in the analysis.

However, there are some limitations in the study. The instruments were not normed and validated in our setting. This may have affected the outcomes of the children in general. The assumption of cultural inappropriateness reducing the outcomes of neuro-psychological tests was described in several studies [39, 79, 80].

We still consider the manuscript to be relevant as it shows an association between stunting and poor neuro-psychological outcomes in Burkina Faso. The study raises the need to highlight awareness of risks of poor nutrition on children's neuro-psychological outcomes specially memory, spatial abilities, general cognition, cognitive flexibility, attention and inhibition. Several multisector interventions including health, breastfeeding promotion, complementary feeding, education, agriculture, women empowerment, infrastructure, water, sanitation and hygiene were successfully used to improve child nutrition in low-income countries [81–83]. Joint prevention strategies may then have important roles in reducing poor nutrition and improving neuro-psychological outcomes.

Table 4 Linear regression analysis between stunting and KABC-II, CCT-1 and TOVA neuro-psychological outcomes of children from the PROMISE Saving Brains study in Burkina Faso

	Unstandardized Coefficient[a] (95% CI)	Standardized Coefficient[a] (95% CI)	P value
Memory (Atlantis—KABC-II)			
No stunting			
Stunting	− 7.9 (− 12.3 to − 3.4)	− 0.4 (− 0.6 to − 0.2)	0.001
Visual abilities (Conceptual Thinking—KABC-II)			
No stunting			
Stunting	− 1.1 (− 1.9 to − 0.3)	− 0.3 (− 0.6 to − 0.07)	0.01
Visual abilities (Face Recognition—KABC-II)			
No stunting			
Stunting	− 0.7 (− 1.4 to 0.02)	− 0.2 (− 0.5 to 0.01)	0.06
Memory (Number Recall- KABC-II)			
No stunting			
Stunting	− 0.5 (− 1.0 to − 0.07)	− 0.3 (− 0.5 to − 0.04)	0.02
Spatial abilities (Triangle—KABC-II)			
No stunting			
Stunting	− 1.1 (− 1.7 to − 0.5)	− 0.4 (− 0.6 to − 0.2)	0.001
Reasoning (Block Counting—KABC-II)			
No stunting			
Stunting	− 0.7 (− 1.6 to 0.2)	− 0.2 (− 0.4 to 0.04)	0.11
General cognition (KABC-II)			
No stunting			
Stunting	− 13.2 (− 19.7 to − 6.8)	− 0.5 (− 0.6 to − 0.2)	≤ 0.0001
Cognitive flexibility (CCT-1)			
No stunting			
Stunting	1.8 (0.02 to 3.5)	0.2 (0.003 to 0.5)	0.04
Attention (TOVA)			
No stunting			
Stunting	− 0.2 (− 0.3 to − 0.02)	− 0.2 (− 0.5 to − 0.03)	0.02
Inhibition (TOVA)			
No stunting			
Stunting	4.6 (0.5 to 8.8)	0.3 (0.03 to 0.5)	0.02

[a] Adjusted for age, sex, schooling, playing, father education, mother employment and EBF (N = 499 for KABC-II & CCT-1 and N = 481 for TOVA)

Conclusion

Stunting is associated with poorer neuro-psychological outcomes among children in rural Burkina Faso. Initiatives related to prevention need to be established and advice on nutrition need to be provided.

Additional file

Additional file 1. Crude coefficient from linear regression between covariates and the neuro-psychological outcomes.

Authors' contributions
ASS, AHD, PH, VN, IMSE, GN, JT, NM, TT and EKA contributed to study concept and design, acquisition of data. ASS, AHD, PH and VN were involved in statistical analysis. ASS, AHD, PH, VN, IMSE, TT and EKA contributed to interpreting the results and drafting of the manuscript. JT and NM were the Principal Investigators of the PROMISE Saving Brains study. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Consent for publication
Not applicable.

Ethics approval and consent to participate
We obtained a written informed consent from all the care-takers and an oral assent from the children. The Institutional Review Board (IRB) of Centre MURAZ has approved the study number 008-2013/CE-CM.

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III

PLOS ONE

RESEARCH ARTICLE

Effects of schooling on aspects of attention in rural Burkina Faso, West Africa

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Abstract

Background

We aimed to study the effects of schooling on aspects of attention using the Test of Variables of Attention (TOVA) among children in rural Burkina Faso.

Methods

We re-enrolled children of a previously community-based cluster randomized exclusive breastfeeding trial in rural Burkina Faso. A total of 534 children (280 boys and 254 girls) aged 6 to 8 years were assessed using the TOVA. We examined the effect size difference using Cohen's d, ANOVA and conducted regression analyses.

Results

Forty nine percent of the children were in school. Children not in school performed poorly with a small effect size difference for 'Response Time', 'Errors of omission', and 'Errors of commission' compared to children in school. The effect size difference was moderate for 'Response Time Variability', and 'D prime score'.

Conclusion

Schooling affects different aspects of attention in rural Burkina Faso. In settings where literacy and schooling rate is low, public sensitizations of the benefits of schooling need to be reinforced and advice on sending children to school need to be provided continuously.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Attending school is important in child development and is associated with health and increased earnings of offspring [1,2]. It has strong impact on health, life chances, survival, development and children who do not complete school or repeat grades are at the greatest risk [3,4].

However, 59 million school age children do not receive formal education worldwide [5,6] and sub-Saharan Africa has the lowest rate [7]. In Burkina Faso, the net attendance ratio of primary school participation is 50% for female and the enrolment ratio of pre-primary school participation is 4% [7].

Tracking the neurodevelopment of children such as attention irrespective of their exposure to formal education is complicated by the strong association between schooling and performance on neuropsychological measures; several studies using tests administered by human examiner show that neuro-developmental outcomes of children attending school is improved compared to unexposed [8–13].

This paper stemmed from the PROMISE Saving Brains (SB) study, which was a follow-up study of the PROMISE EBF cohorts in Uganda and Burkina Faso [14]. The primary objective of the PROMISE SB study was to assess the long-term effect of exclusive breastfeeding promotion by peer counsellors in Uganda and Burkina Faso, on cognitive abilities, emotion-behaviour-social symptoms, school performance and linear growth among 5–8 years old children. The study showed only small and not significant differences in the outcomes and concluded that peer promotion for exclusive breastfeeding in Burkina Faso and Uganda was not associated with differences in cognitive abilities, emotion-behaviour-social symptoms, school performance and linear growth when children reach school age [15].

Based on the data collected in the PROMISE SB study in Burkina Faso, we explored the effects of schooling on attention in settings where literacy and school attendance is low. To measure attention, we used the Test of Variables of Attention (TOVA) which has similarities with the d2 Sustained-Attention Test [16]. The TOVA is a computerized test measuring attention, that has been used to explore multiple health and developmental risks in the exploration of attention [17–23]. In Africa, the TOVA was used to study attention deficit among children with early cerebral malaria in Senegal [24], and HIV infected children in Uganda [25,26].

Materials and methods

Study area, setting, study design and participants

Burkina Faso is a West African low income country. The population aged 0–14 years is 46.3% and 70.1% resides mainly in rural areas [27,28]. The literacy rate is among the lowest in the world [29].

In 2006, a community-based cohort of children was established through The PROMISE Exclusive Breastfeeding (EBF) study in rural Burkina Faso [14,30–32]. The sampling was described [14]. From 2013 to 2015, a study was conducted through the PROMISE Saving Brains study to assess the neuro-cognitive performance of the children from the original cohort who had attained 6–8 years of age; the children from the initial PROMISE EBF trial who were found to be alive and still resident in the study area were re-enrolled as described in detail previously [33].

Outcome measures

The visual Test of Variables of Attention (TOVA) is an individually administered computerized continuous performance test developed to assess attention in normal and clinical populations. To measure attention in our study, we used the following variables:

- **Response time** (in milliseconds): this score is the measure of the average time it takes for the subject to respond correctly to a target. It is considered as a measure of speed of responding and the reactivity of the subject. A lower 'Response time' equates with a faster speed of responding and a swifter reactivity of the subject.
- **Response time variability**: this score is a measure of the variability in the subject's response time on accurate responses; it is considered as a measure of consistency in the speed of responding. The lower 'Response time variability' the more consistent is the performance of the subject.
- **Errors of omission**: this score is measured as the failure to respond to the target stimulus. 'Errors of omission' scores are considered to be a measure of inattention. Fewer 'Errors of omission' equates with less observed inattention in the subject.
- **Errors of commission**: this score is measured as an inappropriate response to the non-target stimulus. 'Errors of commission' scores are considered to be a measure of impulsivity. The higher the 'Errors of commission' the more impulsive is the subject's behaviour.
- **D prime score**: this score is a response sensitivity score and is interpreted as a measure of accurate performance over time. The higher the 'D prime score' the greater is the accuracy over time of the subject [25,34–36].

A summary of the calculation's methods and the scores' description is presented in Table 1.

The test was normed on children and adults, ages 4 to 80+ years and all norms are differentiated by age and gender [33]. The test duration is 22 minutes and the total test time (T) is divided in 4 quarters: quarter 1 (Q1), quarter 2 (Q2), quarter 3 (Q3), and quarter 4 (Q4) and 2 halves, half 1 or H1 where target stimuli are less frequent, and half 2 or H2 where target stimuli are more frequent. The total score reflects subject's performance over the entire test. Each target stimulus is presented for 100 ms every 2 seconds. In total, 324 target stimuli are presented during the entire test. The target is presented in 22.5% (n = 72) during the first half of the test (stimulus infrequent condition 1) and 77.5% (n = 252) during the second half (stimulus frequent condition 2) [33]. The present study used the TOVA Version 8.1. It was presented on Hp Probook 4540s laptop computers in which Windows 8 was installed. These laptops have 15.6 inches screens for a clear view of the stimuli.

The TOVA was individually administered by a team of four psychologists. The instructions were translated in the main local language (Dioula) commonly spoken in the study area. Independent back translations were completed prior to administration to check clarity and

Table 1. Calculation methods and score description in the TOVA test.

Score	Calculation methods	Calculation formula*	Description
Total response time	Average of the correct response times	$\frac{\sum(\text{Correct Response Times})}{\text{Correct Responses}}$	Measure of speed of responding and the reactivity
Total response time variability	Standard deviation of the mean correct response times	$\sqrt{\frac{(\sum_{i=0}^{n}(x_i - \text{Mean Correct RT})^2)}{(\text{Correct Responses})}}$	Measure of consistency in the speed of responding
Total errors of omission	Number of correctly responds to the stimuli	$\frac{\text{Omissions}}{(\text{Targets} - \text{Anticipatories})} x100$	Measure of inattention
Total errors of commission	Number of incorrectly responds to the non stimuli	$\frac{\text{Commissions}}{(\text{NonTargets} - \text{Anticipatories})} x100$	Measure of impulsivity
D prime score	Accuracy of stimuli and non stimuli discrimination	$z\left(\frac{\text{Commission Percentage}}{100}\right) - z\left(1 - \left(\frac{\text{omission Percentage}}{100}\right)\right)$	Accurate performance over time

*All the calculations are done by the computer and the results are directly given

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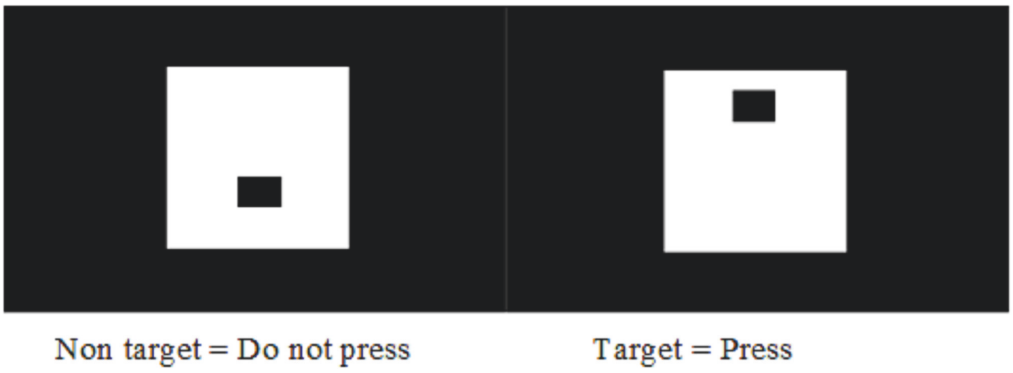

Fig 1. Indication of non target and target in visual TOVA.

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veracity. The children were randomly assigned to the different administrators for assessment. Children sat in a quiet room at roughly 75 cm away from the laptop. They were instructed to respond by pressing a hand-held micro switch whenever the target stimulus appears, and not to respond when the non-target stimulus is shown on the screen (Fig 1) [34].

Before starting the TOVA test, a practice which lasts 3 minutes was conducted. Instructions were given until the child understood and passed the practice test. The test-retest reliability of the TOVA is satisfactory after 90 minutes and highly stable after one week [33]. Children were retested on a different day when the test was interrupted.

Exposure measure

Information about schooling (child attends school yes/no) was collected in a household interview with the caretaker in the same week and prior of the neuro-cognitive assessment. Data collectors approached each child's household to administer a questionnaire to the child's caregiver during a one-to-one interview. Mothers were the primary respondents, and responses were verified at the school. Of the 534 children included in this survey, 263 (49.3%) were not in school.

Covariates

In the interview, questions were asked about additional background characteristics that may influence the child's performance. These included the child's age, child's access to play materials in the home, whether children had been exposed to corporal punishment in the last 12 months, the employment/occupation of the child's father and of the mother (dichotomized to unemployed = no revenue/ farmer, or employed), the education of the father and of the mother (dichotomized to educated = at least one year in school, or not educated), mother's age, mother's depression status using the Hopkins symptom checklist [37] (dichotomized to depression = at least a symptom in the checklist, no depression = no symptom in any of the checklists), and presence of electricity in the compound. Questions regarding past hospitalizations since birth of the child, history of cerebral malaria, were also asked and anthropometric data (height, age) were measured according to standard procedures [38] by a paediatrician at the study site. Stunting was defined as below -2 standard deviations of height-for-age. Information on breastfeeding practices was retrieved from the records of the PROMISE EBF trial.

Field-testing and piloting of all the instruments was conducted prior to data collection to calibrate and standardize the assessment of cognitive measures and the data collection. The psychologists underwent field training and refresher training to standardize the administration of the TOVA on local children prior to the study participants.

Statistical analysis

Statistical analyses were conducted in several stages using methodologies that were described in detail previously [33]:

1. To examine within population variance, the distribution of scores (mean, standard deviation, median, minimum, maximum, skewness and kurtosis) were used. Covariates differences by schooling were tested using chi square analyses. Box-and-whisker plots were used to illustrate the children's errors on the TOVA. Extreme scores were winsorized to discount the influence of outliers by replacing their values with the nearest scores within this range.
2. Pearson product-moment coefficients (r) were computed to examine the intercorrelation between the test and the reliability as reported in the TOVA manual through the assessment of the degree of agreement among various test portions, appropriate for measuring reliability for timed tasks such as the TOVA [34].
3. The association between child's schooling and TOVA attention measures were examined through ANOVA, linear regression and effect size differences (Cohen's d) [39,40]. A bivariate analysis between potential confounders including age, sex, stunting, past hospitalization, corporal punishment, fathers' education and mothers' employment [8,10,12,41] and the promotion of exclusive breastfeeding ('intervention arm' of the initial trial) and the outcome was conducted. All statistical tests were two-sided and declared significant at the 5% level. STATA 13 was used to perform the analysis.

Ethical considerations

The PROMISE SB study was approved by the Institutional Review Board of Centre MURAZ, BP 390 Bobo-Dioulasso, Burkina Faso number 008-2013/CE-CM on 4th April 2013. Written informed consent was obtained from all caretakers in the study and oral assent was obtained from the children.

Results

Study population

As described in detail previously [33], of the original 794 children enrolled in the PROMISE EBF study in Burkina Faso, 561 were found alive and re-consented for the follow-up study; 534 children completed the TOVA and had information on their schooling status (Fig 2).

Of these, 50.7% (271/534) were at school and 52.4% (280/534) were boys. The mean (±*SD*) age at assessment was 7.2 (±0.4 years), the median (IQR) was 7.2 (6.9–7.4) years, with a range of 6.3 to 8 years. The mean (±*SD*) age of the mothers at assessment was 33.4 (±6.3 years) and none of them was educated. Of the fathers, 30.5% (151/495) had attended school and 13.2% (66/500) were in employment. Three quarters of the compounds reported having electricity 77.2%, (386/500) (Table 2). The majority of them had solar power and were not connected to the grid.

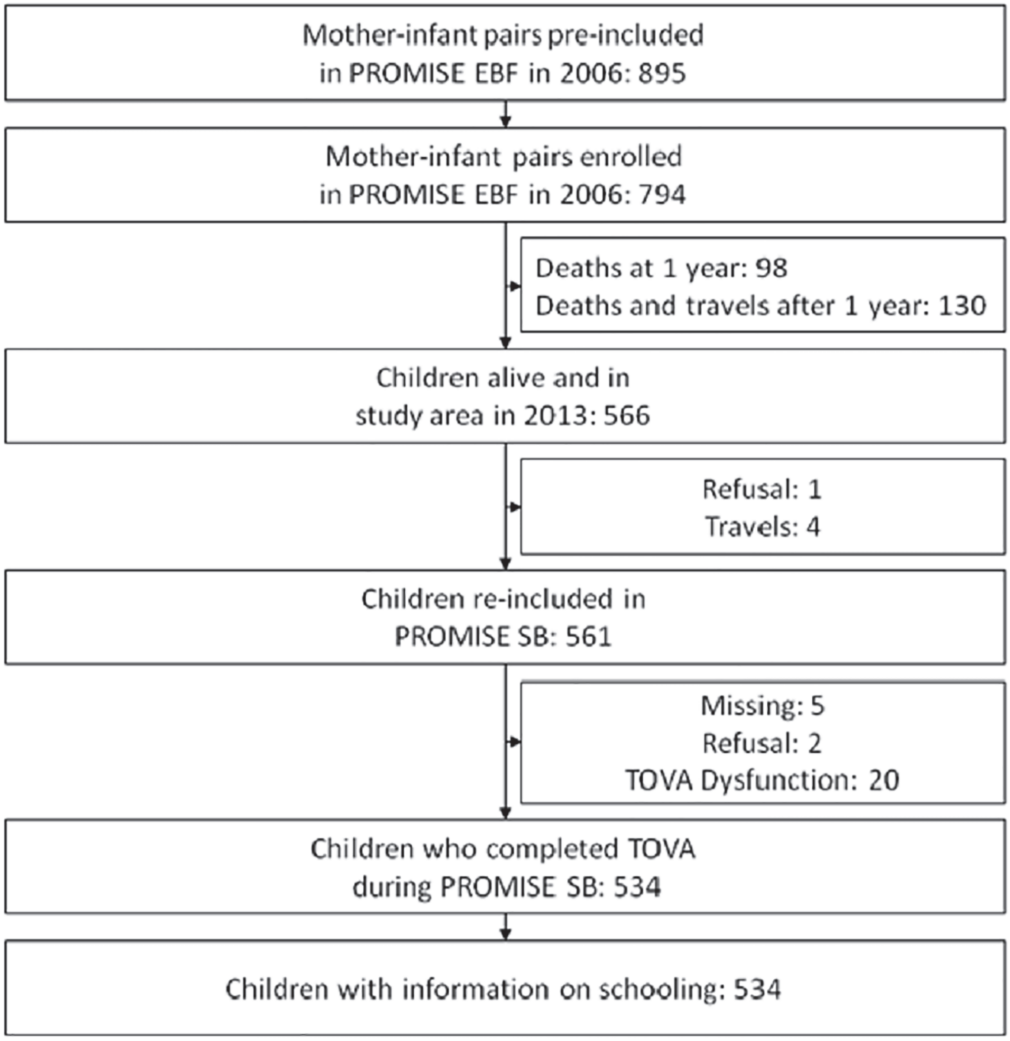

Fig 2. Study profile of children who completed the TOVA and having information on schooling at the PROMISE Saving Brains study in rural Burkina Faso.

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On the TOVA, the total mean score was 725.5 ± 130.7 for 'Response time', 257.9 ± 57.7 for 'Response time variability', 78.0 ± 57.5 for 'Errors of omission', 27.5 ± 16.5 for 'Errors of commission', and 2.3 ± 0.6 for 'D prime score' (Table 3). The range was 443.6–1102.4 for 'Response Time', 121.3–432.0 for 'Response time variability', 1–254 for Errors of omission', 0–73 for 'Errors of commission', and 0.5–4.1 for 'D prime score'. Within each condition, the data indicated a moderate (r ranges from 0.5 to 0.79) to high reliability ($r \geq 0.8$) between quarters, halves

Table 2. Description of the children who completed the TOVA from the PROMISE Saving Brains study in rural Burkina Faso.

	Total, N = 534 N (%)	Child in school 271 (50.7) N (%)	Child not in school 263 (49.3) N (%)	P value
Age Mean ± *SD* (in years)	7.2±0.4	7.2±0.3	7.2±0.4	0.15
Mothers age Mean ± *SD* (in years)	33.4 ± 6.3	33.3 ± 6.4	33.5 ± 6.2	0.71
Promotion of Exclusive Breastfeeding				0.01
No	283 (53.0)	130 (48.0)	153 (58.2)	
Yes	251 (47.0)	141 (52.0)	110 (41.8)	
Sex				0.08
Boys	280 (52.4)	132 (48.7)	148 (56.3)	
Girls	254 (47.6)	139 (51.3)	115 (43.7)	
Stunting (< -2 *SD* in height-for-age)				0.005
No	435 (84.8)	232 (89.2)	203 (80.2)	
Yes	78 (15.2)	28 (10.8)	50 (19.8)	
Child has been hospitalized				0.008
No	395 (77.2)	188 (72.3)	207 (82.1)	
Yes	117 (22.8)	72 (27.7)	45 (17.9)	
Child has history of cerebral malaria				0.55
No	435 (91.6)	218 (90.8)	217 (92.3)	
Yes	40 (8.4)	22 (9.2)	18 (7.7)	
Child plays with object at home				0.32
No	263 (52.6)	127 (50.4)	136 (54.8)	
Yes	237 (47.4)	125 (49.6)	112 (45.2)	
Child received corporal punishment in the last 12months				0.49
No	477 (95.4)	242 (96.0)	235 (94.8)	
Yes	23 (4.6)	10 (4.0)	13 (5.2)	
Father employed				0.02
Yes	66 (13.2)	42 (16.7)	24 (9.7)	
No	434 (86.8)	210 (83.3)	224 (90.3)	
Father educated				0.99
Yes	151 (30.5)	76 (30.5)	75 (30.5)	
No	344 (69.5)	173 (69.5)	171 (69.5)	
Mother employed				0.004
Yes	26 (5.2)	6 (2.4)	20 (8.1)	
No	474 (94.8)	246 (97.6)	228 (91.9)	
Mothers current depression				0.07
No	261 (53.2)	140 (57.1)	121 (49.2)	
Yes	230 (46.8)	105 (42.9)	125 (50.8)	
Electricity in compound				0.33
Yes	386 (77.2)	190 (75.4)	196 (79.0)	
No	114 (22.8)	62 (24.6)	52 (21.0)	

SD: Standard deviation

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and with the entire test ($p<0.001$) with a slightly higher correlation coefficient in half2. The intercorrelations reliability coefficients between TOVA test measures were significant between all the tests except Response time—Errors of commission (r = 0.0322) in condition 1 and Response time variability—Errors of commission ($r = 0.0377$) in condition 2 (Table 4).

Table 3. Population parameters of performance scores in the d2 Sustained-Attention Test.

	Total, N = 534				Child in school, N = 271				Child not in school, N = 263			
	M	*SD*	Skewness	Kurtosis	*M*	*SD*	Skewness	Kurtosis	*M*	*SD*	Skewness	Kurtosis
Total response time	725.5	130.7	0.0002	0.12	701.3	125.7	0.0002	0.58	750.3	131.3	0.09	0.04
Total response time variability	257.9	57.7	0.004	0.98	242.5	50.8	0.32	0.20	273.9	60.1	0.11	0.80
Total errors of omission	78.0	57.6	0.0001	0.80	68.5	52.4	0.0001	0.83	87.8	61.0	0.0001	0.70
Total errors of commission	27.5	16.5	0.0001	0.51	24.8	14.9	0.0001	0.19	30.1	17.6	0.0001	0.69
D prime score	2.3	0.6	0.02	0.83	2.5	0.6	0.04	0.90	2.1	0.6	0.2	0.3

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Table 4. Intercorrelations reliability coefficients between TOVA test measures as reported by children from the PROMISE Saving Brains study in Cascades health district, rural Burkina Faso.

TOVA test conditions	Condition 1				
Condition 2	Response time	Response time variability	Errors of omission	Errors of commission	D prime score
Response time	1	0.64***	0.46***	0.03	-0.27***
Response time variability	0.68***	1	0.44***	0.36***	-0.47***
Errors of omission	0.44***	0.41***	1	0.13**	-0.63***
Errors of commission	-0.38***	0.04	-0.49***	1	-0.52***
D prime score	-0.14**	-0.45***	-051***	-0.38***	1

**<0.01

***<0.001

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Effects of schooling and covariates on attention measures

Children who were not in school were 49.3% (263/534). Children who were not in school performed more poorly on measures of 'Response Time' (mean difference = 49.0 ± 11.1, $p<0.0001$), 'Response Time Variability' (mean difference = 31.4 ± 4.8, $p<0.0001$), 'Errors of omission' (mean difference = 19.3 ± 4.9, $p = 0.0001$), 'Errors of commission' (mean difference = 5.2 ± 1.4, $p = 0.0002$) and 'D prime score' (mean difference = 0.3 ± 0.05, $p<0.0001$) compared to children in school (Table 5). The effect size was small for 'Response Time' (Cohen's $d = 0.38$), 'Errors of omission' (Cohen's $d = 0.33$), and 'Errors of commission' (Cohen's $d = 0.32$). It was moderate for 'Response Time Variability' (Cohen's $d = 0.56$), and 'D prime score' (Cohen's $d = 0.51$) (Table 5). Several covariates including age, sex, stunting, hospitalization and fathers' education were associated with different aspects of attention measures (Table 6).

Table 5. Effect size and bivariate analysis between schooling and TOVA measures of children from the PROMISE Saving Brains study in rural Burkina Faso.

	df	*F*	*P*	Mean difference	Cohen *d*	95% CI (*d*)	Bivariate analysis Crude coefficient (95% CI)	
Total response time	1,532	19.45	<0.0001	49.0 ± 11.1	0.38[$]	[0.21–0.55]	49.1	(27.2–70.9)
Total response time variability	1,532	42.81	<0.0001	31.4 ± 4.8	0.56[$$]	[0.39–0.73]	31.4	(22.0–40.9)
Total errors of omission	1,532	15.40	0.0001	19.3 ± 4.9	0.33[$]	[0.16–0.51]	19.3	(9.6–28.9)
Total errors of commission	1,532	13.84	0.0002	5.2 ± 1.4	0.32[$]	[0.15–0.49]	5.3	(2.5–8.1)
D prime score	1,532	35.88	<0.0001	0.3 ± 0.05	0.51[$$]	[0.34–0.69]	-0.3	(-0.4–-0.2)

[$] Small effect size from 0.2 to 0.49.

[$$] Moderate effect size from 0.5 to 0.79.

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Table 6. Crude coefficient between covariates and the TOVA among children from the PROMISE Saving Brains study in rural Burkina Faso.

	Response time	Response time variability	Errors of omission	Errors of commission	D prime score
Age, N	534	534	534	534	534
Crude	-26.3	-13.9	-15.2	-3.9	0.3
95% CI	-57.8–5.3	-27.9–-0.02	-29.1–-1.3	-7.9–0.02	0.1–0.4
p-value	0.1	0.05	0.03	0.05	<0.0001
Sex, N	534	534	534	534	534
Crude	-26.7	11.0	7.8	1.9	-0.1
95% CI	-48.8–-4.5	1.3–20.8	-1.9–17.6	-0.9–4.7	-0.2 –-0.01
p-value	0.01	0.02	0.1	0.1	0.03
Stunting, N	513	513	513	513	513
Crude	0.4	-8.2	-3.7	5.3	0.2
95% CI	-31.3–32.3	-22.0–5.5	-17.7–10.3	1.4–9.3	0.02–0.3
p-value	0.9	0.2	0.6	0.008	0.02
Hospitalization, N	512	512	512	512	512
Crude	25.3	-13.9	-10.5	2.3	0.09
95% CI	-52.4–1.8	-25.7–-2.2	-22.5–1.4	-1.1–5.7	-0.04–0.2
p-value	0.06	0.02	0.08	0.1	0.1
Corporal punishment, N	500	500	500	500	500
Crude	40.7	-3.2	2.8	-6.1	0.06
95% CI	-14.8–96.2	-27.5–21.1	-21.5–27.2	-13.0–0.7	-0.2–0.3
p-value	0.1	0.7	0.8	0.08	0.6
Father educated, N	495	495	495	495	495
Crude	-31.4	-10.5	-12.0	0.01	0.1
95% CI	-56.8–-6.2	-21.6–0.6	-23.1–-0.9	-3.1–3.2	-0.02–0.2
p-value	0.01	0.06	0.03	0.9	0.09
Mother's employment, N	500	500	500	500	500
Crude	-6.2	6.4	-15.6	1.6	0.1
95% CI	-58.7–46.2	-16.5–29.3	-38.5–7.4	-4.8–8.1	0.1–0.4
p-value	0.8	0.5	0.1	0.6	0.3
Promotion of EBF N	534	534	534	534	534
Crude	0.2	3.4	2.9	0.8	-0.08
95% CI	22.1–22.5	-6.5–13.2	-6.8–12.8	-2.0–3.6	-0.2–0.03
p-value	0.9	0.5	0.5	0.5	0.1
	Response time	Response time variability	Errors of omission	Errors of commission	D prime score
Age, N	534	534	534	534	534
Crude	-26.3	-13.9	-15.2	-3.9	0.3
95% CI	-57.8–5.3	-27.9–-0.02	-29.1–-1.3	-7.9–0.02	0.1–0.4
p-value	0.1	0.05	0.03	0.05	<0.0001
Sex, N	534	534	534	534	534
Crude	-26.7	11.0	7.8	1.9	-0.1
95% CI	-48.8–-4.5	1.3–20.8	-1.9–17.6	-0.9–4.7	-0.2 –-0.01
p-value	0.01	0.02	0.1	0.1	0.03
Stunting, N	513	513	513	513	513
Crude	0.4	-8.2	-3.7	5.3	0.2
95% CI	-31.3–32.3	-22.0–5.5	-17.7–10.3	1.4–9.3	0.02–0.3
p-value	0.9	0.2	0.6	0.008	0.02
Hospitalization, N	512	512	512	512	512
Crude	25.3	-13.9	-10.5	2.3	0.09

(*Continued*)

Table 6. (Continued)

95% CI	-52.4–1.8	-25.7–-2.2	-22.5–1.4	-1.1–5.7	-0.04–0.2
p-value	0.06	0.02	0.08	0.1	0.1
Corporal punishment, N	500	500	500	500	500
Crude	40.7	-3.2	2.8	-6.1	0.06
95% CI	-14.8–96.2	-27.5–21.1	-21.5–27.2	-13.0–0.7	-0.2–0.3
p-value	0.1	0.7	0.8	0.08	0.6
Father educated, N	495	495	495	495	495
Crude	-31.4	-10.5	-12.0	0.01	0.1
95% CI	-56.8–-6.2	-21.6–0.6	-23.1–-0.9	-3.1–3.2	-0.02–0.2
p-value	0.01	0.06	0.03	0.9	0.09
Mother's employment, N	500	500	500	500	500
Crude	-6.2	6.4	-15.6	1.6	0.1
95% CI	-58.7–46.2	-16.5–29.3	-38.5–7.4	-4.8–8.1	0.1–0.4
p-value	0.8	0.5	0.1	0.6	0.3
Promotion of EBF N	534	534	534	534	534
Crude	0.2	3.4	2.9	0.8	-0.08
95% CI	22.1–22.5	-6.5–13.2	-6.8–12.8	-2.0–3.6	-0.2–0.03
p-value	0.9	0.5	0.5	0.5	0.1

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Discussion

In the present study, we observed an association between children being in school and better attention as measured by the 'Response time', the 'Response time variability', the 'Errors of omission', the 'Errors of commission' and the 'D prime score' of the TOVA computerized neuropsychological performance test among children aged 6 to 8 years in rural Burkina Faso compared to children in school.

Our study was conducted in an African context where it is not uncommon for school age children to not be in school. All the children were from the general population in rural areas in Burkina Faso and were previously part of a community-based cluster randomized trial which assessed the promotion of exclusive breastfeeding [14]. These results were supported by the evidence of sensitivity to within population variance and robust reliability of the TOVA in our context. In its first application in the country, we found variation in performances in the TOVA measures. Children were positively engaged in carrying out the test.

Concerning test reliability, the comparison of scores on test sections quarters, halves for both stimulus infrequent and frequent condition with the total scores was highly comparable to the data reported in the TOVA manual [34]. The reliability coefficient on half 2 was slightly higher relative to the reliability coefficient on half 1. This might be explained by the practice effects obtained from completing the first half, as also found in other studies [17,20]. Also, the correlation coefficients indicate that some of the TOVA measures are not sufficiently reliable, which is particularly true for the Response time variability score. This is consistent with other research; For example, a study found that the performance variability measures in the d2 attention test should be interpreted with caution as they lack reliability [16]. Another study demonstrated (by means of simulation analysis on grounds of classical test theory) that measures of performance variability can never achieve the same degree of reliability as compared to measures of central tendency (i.e., mean scores) [42].

In and not-in school children had the same mean age. The differences found between schooled and unschooled children is consistent with the effects of schooling seen in the performance on non-computerized neuropsychological measures [10,11,13].

The mechanisms in the literature potentially underlying the effects of schooling on attention measures can be divided into three categories: the global effects, the specific effects and the test-taker effects. The aspect of (1) global effect on attention abilities is the measurement intention of psychometric test such as TOVA and is based on instructional experience [43,44]. As soon as children start school, they are required to sit still in order to make progress with learning the cultural techniques (reading, writing, arithmetic), they learn to focus their concentration on relevant aspects for a certain period of time; They learn to concentrate and to resist distractions in terms of a general ability. Studies showed that school attendance measured more finely by additional days in school have been associated with increase scores of intelligence tests [8,10–13,41,45,46]. School exposure has also been associated with other beneficial effects on brain development [10] and yields important development benefits and improves health, earning, human capital [47–50]. However, the interpretations are post hoc and cannot be validated in the study.

The aspect of (2) specific effects is based on the constant and repeated exercise of these cultural techniques which lead to the development of specific skills; this might also contribute to the observed performance differences between the groups and is not entirely avoidable.

The aspect of (3) test-taker effects is based on the understanding of what is being demanded of them. Studies show that exposure of children in school to the process of receiving and using instructions for learning and education improves test performance by increasing the understanding of the test taker of what is being demanded of them [51,52]. In our study, the instructions were given by trained and experienced psychologists. We consider this as a strength of our study as recent research has pointed on the importance to verbally explain task requirement and to instruct the participants to give their best possible performance, in contrast to written instructions. By this means, the experimenter is able to obtain immediate feedback from the participant, and if necessary, can deliver further explanation to ensure that they have understood the instruction correctly [53]. The assessment in our study was based on a standardized computerized measure of attention for children which has been used in Africa [24–26]. In fact, studies suggest that computerized neuropsychological performance tests provide many advantages over tests administered by a human examiner. Observed increases in reliability and validity [54,55] stem from a reduction in human error [56], increased ease of administration [57], less time devoted to the preparation of the materials, reduction in errors during scoring [58], increased accessibility for specific populations [59], ability to measure performance on time-sensitive tasks, and automated data exporting [56,60].

The study has some limitations. The participants were part of an established community-based cohort of children as described in detail previously [14,30–33]. Given the non-random selection of schooled and un-schooled children in the general population, selection bias should not be omitted. In our study, we experienced equipment malfunction mainly due to power shortages, with a difficulty to reschedule the children for another TOVA assessment; the missing values on TOVA were, however, random. A specific limitation of the uses of TOVA in similar contexts is related to the need for special equipment, a secured area for testing, which requires a constant electricity supply. Another limitation is the lack of information on the overall validity of the measure which was used for the first time in our context.

We still consider this paper to be important as it highlights the need to raise awareness of the benefits of schooling in rural contexts without implying a causal link between schooling and cognitive performance. Due to the large number of factors simultaneously affecting cognitive performance in children in Africa, we cannot completely isolate the true effect of schooling

from other influences as there are a multitude of potential covariates that naturally cannot be controlled in the present study. However, in the context of schooling, teachers and educators may have an important role in advising the public on its potential benefits. Sensitization initiatives need to be reinforced and advice on sending children to school need to be provided continuously. This study also continues to highlight the need to address educational experience in analyzing and interpreting child neuropsychological performance indicators. Those working in areas where compulsory education exists and is well followed may fail to take into account the consistent effect that schooling has on test performance. Hence, this study might be considered a valuable contribution to our knowledge as it addresses severely neglected aspect which deserves serious attention in the future.

Conclusion

Schooling affects different aspects of attention in rural Burkina Faso. In settings where literacy and schooling rate is low, public sensitizations of the benefits of schooling need to be reinforced and advice on sending children to school need to be provided continuously.

Supporting information

S1 File. Schooling and attention measure dataset.
(ZIP)

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