How Do Maternal Deficiencies in Vitamin B-12 and Vitamin B-9 (Folate) Influence the Neurological Development (Cognitive, Psychological) of Their Offspring?

By Helen Lu

ABSTRACT

Vitamin B plays an important role in the methylation of DNA to help regulate gene expression, especially in children experiencing rapid cell growth phases, such as pregnant women or young children. In addition, folate deficiency in the periconceptional period can contribute to neural tube defects, while vitamin B12 deficits have been associated with acute megaloblastic anemia. This research examines the relationship between maternal plasma vitamin B levels with their children and the long-term impacts of deficits in vitamin B to the cognitive abilities of pattern reasoning, verbal fluency, and memory retrieval as a few examples of how their cognitive and psychological developments are assessed. Further investigations should focus on the specific genes potentially muted due to vitamin B deficiency and examine how to prevent folate vitamin B12 deficiency in developing/third world countries.

Keywords: *Malnutrition, Vitamin B12, Vitamin B12 Deficiency, Folate, Folate Deficiency, Cognitive Development, Maternal Folate, Psychological Development*

INTRODUCTION

Malnutrition is caused by several economic, geographical, and social challenges families face, especially in Sub-Saharan Africa and small Middle Eastern countries (Roser and Ritchie (1)) malnutrition is closely linked to many micronutrient deficiencies such as vitamin B-12 and B-9 (folate), hindering the child's ability to reach targeted cognitive and psychological milestones.

One of the primary micronutrient deficiencies is vitamin B-12, an essential water-soluble compound obtained from food. For example, vitamin B-12 is commonly found in animal-sourced food such as beef liver, mollusks, clam, veal, and dairy products ("FoodData Central"). This vitamin is vital for the development, myelination and functioning of the central nervous system. In addition, vitamin B-12 acts as a cofactor for synthesizing methionine, an amino acid used with cysteine (a sulphur-containing amino acid) to produce protein tissues, which is important during fetal development to ensure proper gene expression and cell differentiation (Phillips). Another highly deficient micronutrient is vitamin B-9 (folate). Folate regulates the production of genetic material such as DNA and the division of cells. Deficiencies in vitamin B-12 may interrupt metabolic processes and lead to megaloblastic anemia. At the same time, inadequate folate supplementation during pregnancy may result in conditions like neural tube defects in newborns ("Spina Bifida"). Therefore, vitamin B-12 and folate are essential for individuals experiencing rapid cell growth phases, such as pregnant women or young children ("Vitamin B-12") ("Folate").

Nowadays, folate deficiency is rare in North America and Asia but highly prevalent in Sub-Saharan Africa, where access to foods and supplements is expansive and scarce. Whereas US citizens consume folic acid, those in rural regions of Africa may lack access to such supplements. In this research, we conducted a meta-analysis of 9 studies to gain a better understanding of how maternal folate deficiency affects the cognitive development of their offspring in Africa.

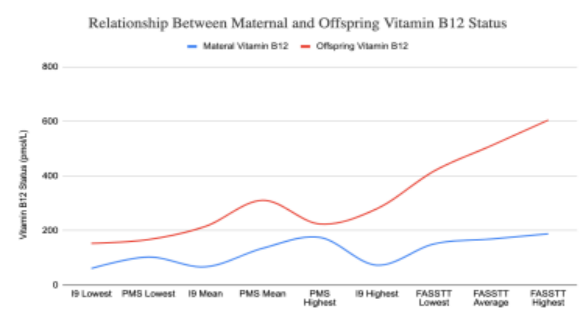
RESEARCH METHODOLOGY

Nine research studies that examine the impact of maternal vitamin B-12 and folate deficiencies on their offspring's neurological development were acquired through PubMed. Cognitive and psychological tests were used to assess the child's brain development for the frontal lobe (emotion, cognitive, short-term memory) and the temporal lobe (auditory information, long-term memory).

Here, we specifically analyzed studies from countries with the highest prevalence of micronutrient deficiencies in children: namely, in Africa and South Asia (Roser and Ortiz Ospina) (Roser and Ritchie (1)) (Ritchie and Roser (2)), with medical reports from these regions within the last 20 years (blood plasma probe for detecting micronutrients was only invented in 2004 (Adámek et al.)). In addition, we restricted the age of pregnant mothers to 20-40 to limit the likelihood of other abnormal diseases in mothers influencing the cognitive scores in children. The essay majorly examines the relationship between vitamin deficiency and cognitive development, but it will also examine the correlation between maternal and children vitamin deficiencies and the evidence in numbers for the consequence of maternal deprivation of vitamin B (12 and 9).

DATA

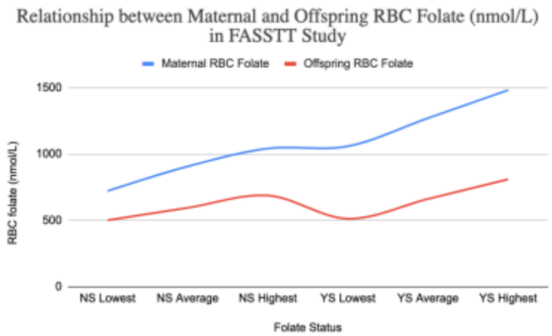
The Relationship between Maternal Plasma Vitamin B-12 (ng/mL) and Offspring Vitamin B-12 (ng/mL)



**I9: Higher Maternal Plasma Folate associated with better cognitive function scores in 9–10-year-old children in South India*
***PMS: Pune Maternal Study*
****FASSTT: Effects of maternal folic acid supplementation during the second and third trimesters of pregnancy on neurocognitive development in the child: an 11-year follow-up from a randomized controlled trial*

Effects of maternal folic acid supplementation during the second and third trimesters of pregnancy on neurocognitive development in the child: an 11-

year follow-up from a randomized controlled trial (FASSTT)



NS: No supplementation; YS: Yes supplementation (of folic acid)

<u>Group Studied:</u>

This study was a follow-up investigation in 11-year-old children whose mother participated in the FASSTT trial in pregnancy. The FASSTT trial contained women aged 18-35 years who were given supplementations of 400ug folic acid/day or a placebo until the end of their pregnancy.

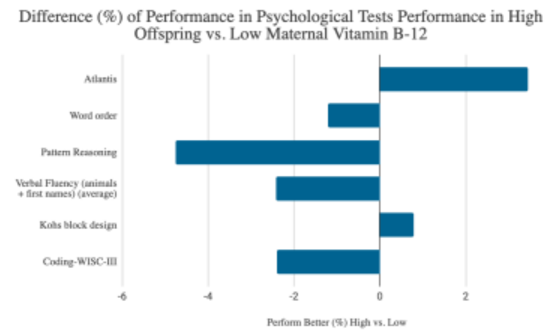
<u>Methods:</u>

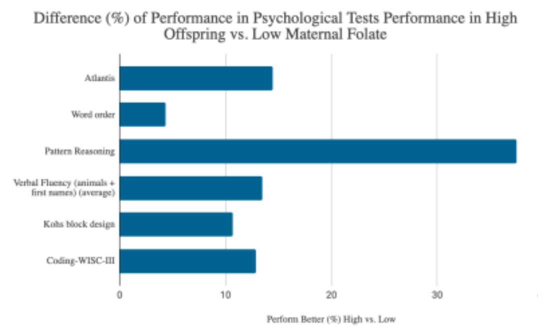
For B-Vitamin measurements in the mothers, non-fasting blood samples were collected at 14th and 36th GW and the umbilical cord blood was collected at delivery. For the children, non-fasting blood samples were collected from a pediatric phlebotomist and processed within 4 hours for serum vitamin B-12.

<u>Limitations:</u>

In the FASSTT trial, 296 women were initially recruited, and 119 mothers completed the full FASST trial. In this follow-up trial, only 68 pairs of mother-child were available for further investigation (placebo n=31, folic acid n=37). The relatively small sample size of mother-child pairs may have limited the ability to detect more differences in the biomarkers of mothers and children for each nutrient collected.

Higher Maternal Plasma Folate associated with better cognitive function scores in 9- to 10-year-old children in South India





<u>Group Studied:</u>

This experiment examined the children aged 9-10 (n=536, boys=259, girls=277) years from the Mysore Partenon study conducted in 1997-1998, which focused on the incidence and effects of short-term and long-term gestational diabetes mellitus impacts on newborns.

<u>Methods:</u>

The child's maternal vitamin B-12 and folate status biomarkers were obtained using maternal blood samples collected at 30 ± 2 week of gestation.

The cognitive assessments tested specific domains in the Carroll model, three core tests from the Kaufman Assessment Battery for children, and other tests adapted to the local cultural context. Specifically, it tests domains of long-term memory and retrieval ability (Atlantis), short-term memory (word order), reasoning ability (pattern reasoning), language production (verbal fluency), visuospatial ability (Kohs' block design), and visuomotor processing and coordination with the WISC-III (coding Wechsler Intelligence Scale for Children-III. (see appendix B for details)

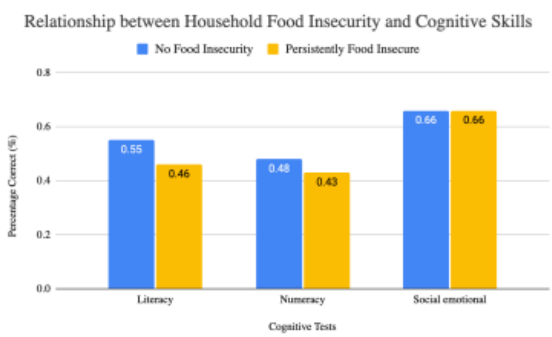
<u>Findings:</u>

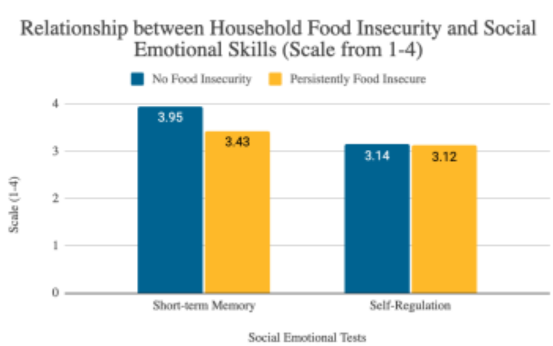
According to Graph 1, the children with higher plasma vitamin b-12 performed better on long-term memory and retrieval (Atlantis) but were weaker in areas of word order, pattern reasoning, verbal fluency, coding-WISC-III. Thus, there is no clear association between the level of plasma v12 concentration to the child's cognitive abilities. Looking at Graph 2, an increase in maternal folate led to higher cognitive scores in children, as children with the highest maternal folate consistently performed better than children with low maternal folate in all tests of cognitive domains, with the most evidence in the increased score performance score of 37.5% concluded by the comparison of scores from higher maternal folate versus low maternal folate (Veena, Sargoor R et al).

Limitations:

Although higher maternal folate led to higher scores from their children, other factors may have contributed. Folate is most commonly found in animal products, which is relatively more expensive compared to vegetables. Thus, the disadvantaged families may have less access to higher-quality foods and meats and a generally lower standard of living, impacting the quality of education that their children receive, contributing to lower cognitive scores.

Household food insecurity and early childhood development: Longitudinal evidence from Ghana





Group Studied:

In this study, over 1300 Ghanian children were tracked over three years to investigate the effects of household food insecurity and deficiencies in nutrients with early childhood development in lower primary schools. The group studied takes place in the most disadvantaged regions of the Greater Accra Region, based on the 2014 UNICEF District League Table. This table indicates the regions in Ghana according to their development of essential services such as education, health, sanitation, and governance.

Methods:

The experiment was conducted at three different time waves: wave 1 (September 2015), wave 2 (May 2017), and wave 3 (May 2018). These children and their caregivers were interviewed via a survey to collect baseline characteristics and data. They assessed the cognitive abilities of children by literacy, numeracy, short-term memory, social-emotional development and self-regulation tests through the Early Grade Reading Assessment (Literacy), the Early Grade Math Assessment (Numeracy), forward digit span tests (short-term memory), subtests from IDELA, and with an adapted version of Preschool Self-Regulation Assessment–Assessor Report (PSRA-AS) (Self-regulation), respectively. Please refer to appendix D for more details.

Findings:

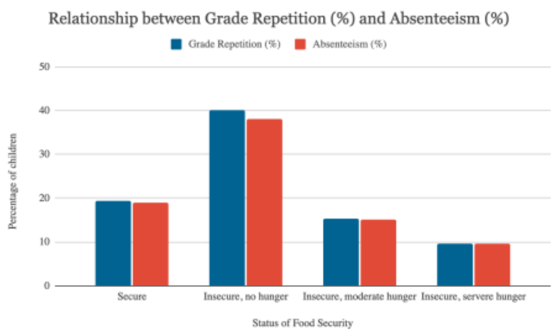
It is seen that most of the children in this study had no food insecurity (n=1116) (84%), and only 44 (3%) children were persistently food insecure. As seen in table 1, children with no food insecurity persistently performed better than those with persistent food insecurity in domains of literacy, numeracy, and short-term memory. However, social-emotional skills and self-regulation skills scored no significant changes or relationship to the child's food security level.

Limitations:

As this study was conducted in the most urbanized city of Greater Accra, the sample group and results may be limited to the sampling frame and selection bias. Additionally, these tests were conducted with children in schools, meaning that children out of school were not assessed, limiting the reliability of the data as not all Ghanian children have the advantage of attending schools.

Vitamin B-12 Deficiency in Children Is Associated with Grade Repetition and School Absenteeism,

Independent of Folate, Iron, Zinc, or Vitamin A Status Biomarkers



Group Studied:

This study was conducted on 2834 children aged 5-12 years of age who were a part of the Bogota School Children Cohort, an investigation on the nutrition and health in public schooled children in Bogota, Columbia. The investigation was carried out in 2006.

Methods:

Information on the baseline characteristics of children was obtained through parental self-administered questionnaires, which included ranking the level of food security by using a scale adapted from the Spanish-language version of the USDA Household Food Security Survey Module and the Community Childhood Hunger Identification project. Fasting blood samples were also obtained at the beginning of the study and processed to identify plasma erythrocyte folate concentrations and plasma vitamin B-12 concentrations.

Parents or caregivers filled records of days children were absent from school during the academic year after enrollment using a diary returned to the researchers weekly. In addition, the number of children who repeated grades was collected after one full year after enrollment. In Bogota's academic system, a child was considered to fail a grade if they failed three subjects, 2 of which were math and language.

Findings:

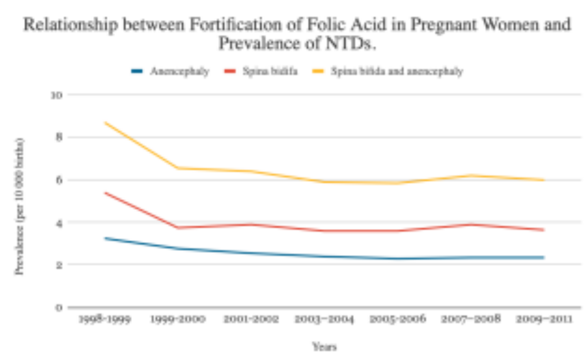
The majority of children studied in this cohort had no food insecurity. Still, a large portion of children was, to some degree, food insecure. According to graph 1, the percentage of children who repeated grades or were absent increased from "no food insecurity" to "food insecure, no hunger" but decreased again as the scale progressed to severe food insecurity.

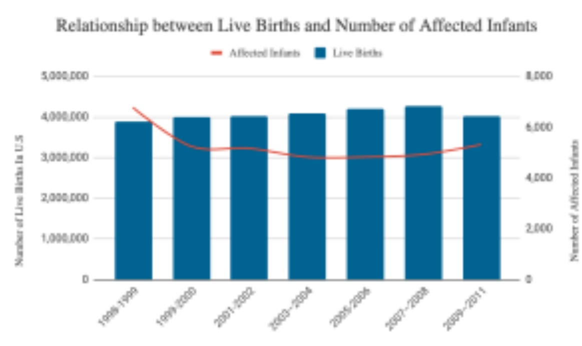
There was also an increase in the days of absence of children with lower vitamin B-12, though no trends were found with the different erythrocyte folate levels.

Limitations:

The intake of vitamin B-12 may not directly correlate and accurately represent the amount absorbed within the body. There is also a possibility of social-economic factors contributing to the higher incidences of grade repetition and absenteeism. Children with poor economic factors may have difficulties obtaining sufficient nutrients for their development and growth, thus impacting their ability to pass academic tests.

Updated Estimates of Neural Tube Defects Prevented by Mandatory Folic Acid Fortification — United States, 1995–2011





Group Studied:

In August 2014, 19 population-based birth defects surveillance programs in the United States reported to CDC for the number of cases of spina bifida and anencephaly, which are common forms of birth defects. In addition, the spina bifida and anencephaly cases were further recorded after the fortification of foods from 1999-2011 for programs with and without prenatal ascertainment for birth defects.

Methods:

All data obtained from CDC Wonder Database (Centers for Disease Control and Prevention).

Findings:

Comparing the number and percentage of birth defects pre and after folic acid fortification, the number has decreased and remained relatively stable across ten years.

EVALUATION

Many studies examined showed a positive relationship between maternal and offspring's folate and vitamin B-12 status. Though vitamin B-12 and folate are both essential micronutrients for the development of the brain, children whose mothers had a high folate measurement performed consistently better in both cognitive and psychological tests, as seen in studies 5 and 6. Similarly, a decrease in folate concentration led to lower test scores and higher-grade repetition (seen in studies 5 and 8). On the other hand, children whose mothers had high vitamin B-12 did not necessarily show an increase in cognitive test scores, meaning that vitamin B-12 likely did not influence the neurological development in children as much as folate did (shown in study 4). Also, while maternal vitamin B-12 deficiency is shown to be closely linked to adverse conditions such as anemia in their offspring, folate deficiency may lead to more life-threatening conditions such as open spina bifida or anencephaly. Folate is involved in DNA methylation. Downstream consequences include psychomotor development and red blood cell (RBC) production (Phillips). Higher maternal folate is associated with beneficial effects on infants' brain and motor development parents who were vegan or vegetarian during pregnancy can result in improper methylation in offspring, which reduces the child's gene expression and reduces the RBC production resulting in anemia and thus hindering their cognitive functions (Kalyan G et al.)

Likewise, as shown by study 5, the group deficient in vitamin B-12 and folate were likely influenced by their mother's nutrient deficiency during pregnancy. In this study, the children whose mothers had low folate status performed 16% lower on psychological tests such as word order and pattern reasoning. Their scores support the conclusion by indicating that the maternal folate level hinders the children's cognitive development.

While folate deficiency is dangerous, an excess intake of folate can be harmful. The recommended amount of folic acid for pregnant women usually is between 0.4mg and 0.9mg (Kennedy and Koren). For example, a study conducted by Paniz et al. showed that mothers who consumed 5mg of folic acid each day during pregnancy were associated with lower neuropsychological outcomes scores in children. This is because the body can only absorb folic acid to a certain extent. Thus, the excess nutrients will accumulate in the bloodstream, forcing other organs such as bone marrow to increase red blood cells' production to absorb the folic acid, resulting in lower numbers and natural killer (NK) cells (Paniz et al.). This change in the number of NK cells reduces the immunological defence system and increases the offspring's susceptibility to oncogenic viruses (Moon and Powis) (Orange).

To lower the prevalence of neural tube defects in children, many countries such as the US, Canada, UK, and Chile began fortifying commonly consumed foods with folic acid (Bailey et al.). For example, in the US, folic acid was directly fortified into flour, cornmeal, rice and other grain products for 140 mcg of folic acid per 100g in 1998. Fortification significantly decreased the number of NTDs in the US (as shown in study 9). However, pregnant mothers would need to supplement with folic acid well before their expected pregnancy as the neural tube closing occurs after 17-30 days after conception (CDC), and any supplements taken after this phase would not be effective.

Conversely, most of the studies were conducted in rural regions in India, Ghana, and Kenya. The living conditions in these countries are different from the United States, thus impacting mothers' ability to obtain adequate micronutrients during pregnancy. For example, study number 8 (Food Insecurity study) shows that many families struggle to be fed every day; hence, mothers cannot consume adequate folic acid. To counteract this issue, the government began fortifying wheat flour with 2.08mg/kg of folic acid and 0.01mg/kg of B-12. However, upon investigation, only 23% of wheat flour was adequately fortified (Nyumuah et al.) Likewise, in India, the government issued flours and grain manufactures to include at least

1.3mg/kg of folic acid and 0.01mg/kg of B-12 (Food Safety and Standards Authority of India and Bakshi). Yet less than 20% of foods produced with a standard for fortification meets national requirements, meaning that it is impossible to consume the required folate levels without supplements (Debadrita Sinclair).

Another factor influencing the mother's micronutrients and the offspring's neurological development is their diet. For example, many regions in India predominantly follow vegetarian or vegan diets due to the limited availability of animal products in average-income families. In a report conducted by the Food Foundation in Pune, almost ¼ children in Pune are stunted, ¼ are wasted, ¼ are underweight (The Food Foundation and Scott). Another study in Pune showed that more than 37% of 210 children that looked healthy between 6 and 23 months of age were deficient in vitamin B-12, thus indicating a strong connection between the offsprings' low vitamin B levels with their culture's predominantly plant-based diet (Kalyan G et al.).

Results in Study 7 further supports the positive correlation between children's cognitive tests scores and their nutritional status from food insecurity. As identified earlier, the maternal vitamin is similar to their offspring's; hence, the food insecure children would signal that their mother was likely deficient in B vitamins. Two factors may contribute to deficiency in mothers: diet and supplement inadequacy. In a study conducted by the University of Ghana, over 53.8 % of women (non-childbearing) are deficient in folate (<10 nmol/L) though Ghanian dishes usually are vegetarian and include vegetable stews with naturally occurring folate found in leafy greens, less than half of the folate content is retained after heating, thereby unchanging the total blood plasma folate concentration (McKillop et al.) (Owusu et al.) (University of Ghana). Furthermore, more than 12% of people in Ghana live below the International Poverty Line with an average GDP per capita of approximately $1743 ("GDP per Capita (Current US$) - Ghana") (Roser and Ortiz-Ospina). Thus, the low income of each household limits the mother's ability to take folic acid supplements as each 100 tablets accounts for 4.6% of their annual income.

Hence, it is unrealistic for households with food insecurity to continuously supplement folic acid during her 40 weeks of pregnancy, preventing the mother from obtaining optimal concentrations of folic acid. Furthermore, education may be hard to enforce when food security is a prominent issue. Together, these factors also explain the positive relationship between grade repetition and absenteeism with increasing hunger from the Botoga study (shown in study 8).

With minimal access to fortified foods and a plant-based diet, it's challenging for pregnant mothers to consume adequate vitamin B-12 and folate. In comparing Pune and US study groups, the difference in vitamin intake differed by 34ng/mL (135ng/mL compared to 169ng/mL, respectively). Hence, the people's food, along with high levels of school absteensim (shown in study 8) and food insecurities (shown in study 7), may have dramatically impacted the offspring's ability to develop critical thinking skills and perform well in the cognitive and psychological tests.

In this study, we analyze the effects of folate with cognitive function and show how vitamin B-12 and folate (B9) can dramatically impact the performance of their offspring in tests, including information retention, pattern recognition, and language proficiency. Thus, pregnant mothers should be monitoring their consumption of folate and other micronutrients to ensure that their offspring's blood nutrient is not deprived of avoiding conditions such as spina bifida or anencephaly. As we analyzed the experiments, we found a limitation in the relatively small sample sizes, making them inevitable to sampling bias and, hence, increasing the conclusions' uncertainty. However, there was a clear trend with low vitamin B consumption and a lower cognitive score. This conclusion prompts the research for finding the specific genes that may have been muted due to vitamin B deficiency to examine how to prevent folate vitamin B12 deficiency in developing/third world countries.

REFERENCE

Adámek, J., Stöckel, J., Hron, M., Ryszawy, J., Tichý, M., Schrittwieser, R., ... & Van Oost, G. (2004). A novel approach to direct measurement of the plasma potential. *Czechoslovak Journal of Physics*, *54*(3), C95-C99.

Anonymous. (n.d.). 11.1 Folate & Folic Acid, Nutrition Flexbook, Retrieved May 16, 2021, from https://courses.lumenlearning.com/suny-nutrition/chapter/11-1-folate-folic-acid/

Anonymous. (n.d.). Spina Bifida. *Mayo Clinic*. Retrieved May 16, 2021, from https://www.mayoclinic.org/diseases-conditions/spina-bifida/symptoms-causes/syc-20377860

Anemia, M. (2021, Aug 25). NORD (National Organization for Rare Disorders). rarediseases.org/rare-diseases/anemia-megaloblastic.

Anthony, K. (2018). "High Homocysteine Level (Hyperhomocysteinemia). *Healthline Media*, Retrieved Jan 2, 2018, from www.healthline.com/health/homocysteine-levels

Aurino, E., Wolf, S., & Tsinigo, E. (2020). Household food insecurity and early childhood development: Longitudinal evidence from Ghana. *PloS one*, *15*(4), e0230965.

Bailey, L. B., Stover, P. J., McNulty, H., Fenech, M. F., Gregory III, J. F., Mills, J. L., ... & Raiten, D. J. (2015). Biomarkers of nutrition for development—folate review. *The Journal of nutrition*, *145*(7), 1636S-1680S.

Bhate, V. K., Joshi, S. M., Ladkat, R. S., Deshmukh, U. S., Lubree, H. G., Katre, P. A., ... & Yajnik, C. S. (2012). Vitamin B12 and folate during pregnancy and offspring motor, mental and social development at 2 years of age. *Journal of developmental origins of health and disease*, *3*(2), 123-130.

Caffrey, A., McNulty, H., Rollins, M., Prasad, G., Gaur, P., Talcott, J. B., ... & Pentieva, K. (2021). Effects of maternal folic acid supplementation during the second and third trimesters of pregnancy on neurocognitive development in the child: an 11-year follow-up from a randomized controlled trial. *BMC medicine*, *19*(1), 1-13.

Debadrita, S. (2020). Fortifying India: Challenges and Opportunities for Large-Scale Food Fortification in India. *Dalberg*. Retrieved Apr 5, 2020, from https://dalberg.com/our-ideas/fortifying-india-challenges-and-opportunities-for-large-scale-food-fortification-in-india.

Duong, M. C., Mora-Plazas, M., Marín, C., & Villamor, E. (2015). Vitamin B-12 deficiency in children is associated with grade repetition and school absenteeism, independent of folate, iron, zinc, or vitamin a status biomarker. *The Journal of nutrition*, *145*(7), 1541-1548.

Food Safety and Standards Authority of India, & Sunil Bakshi. (2017). GDP per Capita (Current US$) – Ghana [Data Set]. data.worldbank.org/indicator/NY.GDP.PCAP.CD? locations=GH.

Graham, S. M., Arvela, O. M., & Wise, G. A. (1992). Long-term neurologic consequences of nutritional vitamin B12 deficiency in infants. *The Journal of pediatrics*, *121*(5), 710-714. Anonymous. (2021). *Intrinsic Factor*. Retrieved from May 16, 2021, from http://www.vivo.colostate.edu/hbooks/pathphys/digestion/stomach/intrinsic_factor.html#:~:text=Intrinsic%20factor%20is%20a%20glycoprotein,in%20the%20 condition%20pernicious%20anemia.

Hannah, R., & Roser, M. (2017, August). Micronutrient Deficiency. *Our World in Data*. ourworldindata.org/micronutrient-deficiency#anemia-in-children.

Jon, J. (2020, May 21). What to Know about the Temporal Lobe. *Medical News Today*. www.medicalnewstoday.com/articles/temporal lobe#:~:text=The%20temporal%20lobe%20is %20one,conscious%20and%20long%2Dterm %20memory.

Kalyan G, B., Mittal, M., & Jain, R. (2020). Compromised Vitamin B12 Status of Indian Infants and Toddlers. *Food and Nutrition Bulletin*, *41*(4), 430-437.

Koonin, L. M., Smith, J. C., Ramick, M., & Strauss, L. T. (1998). Abortion surveillance— United States, 1995. *Morbidity and Mortality Weekly Report: CDC Surveillance Summaries*, 31-68.

Lücke, T., Korenke, G. C., Poggenburg, I., Bentele, K. H. P., Das, A. M., & Hartmann, H. (2007). Mütterlicher Vitamin-B12-Mangel: Ursache neurologischer Symptomatik im Säuglingsalter. *Zeitschrift für Geburtshilfe und Neonatologie*, *211*(04), 157-161.

McKillop, D. J., Pentieva, K., Daly, D., McPartlin, J. M., Hughes, J., Strain, J. J., ... & McNulty, H. (2002). The effect of different cooking methods on folate retention in various foods that are amongst the major contributors to folate intake in the UK diet. *British Journal of Nutrition*, *88*(6), 681-688.

McNulty, H., Ward, M., Hoey, L., Hughes, C. F., & Pentieva, K. (2019). Addressing optimal folate and related B-vitamin status through the lifecycle: health impacts and challenges. *Proceedings of the Nutrition Society*, *78*(3), 449-462.

National Institutes of Health. (2021, March 29). *Folate*. ods.od.nih.gov/factsheets/Folate HealthProfessional.

National Institutes of Health. (n.d.). *Pernicious Anemia*. https://www.nhlbi.nih.gov/health topics/pernicious-anemia.

National Institutes of Health. (2021, April 6). *Vitamin B12*. ods.od.nih.gov/factsheets/ VitaminB12-HealthProfessional.

Nyumuah, R. O., Hoang, T. C. C., Amoaful, E. F., Agble, R., Meyer, M., Wirth, J. P., ... & Panagides, D. (2012). Implementing large-scale food fortification in Ghana: lessons learned. *Food and nutrition bulletin*, *33*(4_suppl3), S293-S300.

Owusu, M., Thomas, J., Wiredu, E., & Pufulete, M. (2010). Folate status of Ghanaian populations in London and Accra. *British journal of nutrition*, *103*(3), 437-444.

Paniz, C., Bertinato, J. F., Lucena, M. R., De Carli, E., Amorim, P. M. D. S., Gomes, G. W., ... & Guerra-Shinohara, E. M. (2017). A daily dose of 5 mg folic acid for 90 days is associated with increased serum unmetabolized folic acid and reduced natural killer cell cytotoxicity in healthy Brazilian adults. *The Journal of nutrition*, *147*(9), 1677-1685.

Phillips, T. (2008). The role of methylation in gene expression. *Nature Education*, *1*(1), 116.

Roser, M., & Hannah, R. (2019). Hunger and Undernourishment. *Our World in Data.* ourworldindata.org/hunger-and-undernourishment.

Roser, M., & Ortiz-Ospina, E. (2013). Global Extreme Poverty. *Our World in Data*. ourworldindata.org/extreme-poverty.

Seladi-Schulman, Jill. (2020, Apr 20). What to Know about Your Brain's Frontal Lobe. *Healthline Media*. https://www.healthline.com/health/frontal-lobe.

Stollhoff, K., & Schulte, F. J. (1987). Vitamin B 12 and brain development. *European journal of pediatrics*, *146*(2), 201-205.

The Food Foundation & Courtney Scott. (2018). *Pune Nutrition Situation and Stakeholder Mapping*. https://mqsunplus.path.org/resources/pune-nutrition-situation-and-stakeholder mapping.

University of Ghana, GroundWork, University of Wisconsin-Madison, KEMRI-Wellcome Trust, UNICEF. (2017). *Ghana Micronutrient Survey 2017*. https://groundworkhealth.org/ wp-content/uploads/2018/06/UoG-GroundWork_2017-GHANA-MICRONUTRIENT SURVEY_Final_180607.pdf

U.S. Department of Agriculture. (2021, Apr 21). *FoodData Central* [Data Set]. fdc.nal.usda.gov/fdc-app.html#/?component=1178.

Watson, E., Olin-Sandoval, V., Hoy, M. J., Li, C. H., Louisse, T., Yao, V., ... & Walhout, A. J. (2016). Metabolic network rewiring of propionate flux compensates vitamin B12 deficiency in C. elegans. *Elife*, *5*, e17670.

Wighton, M. C., Manson, J. I., Speed, I., Robertson, E., & Chapman, E. (1979). Brain damage in infancy and dietary vitamin B12 deficiency. *Medical Journal of Australia*, *2*(1), 1-3.