Effect of iodine and iron supplementation on physical, psychomotor and mental development in primary school children in Malawi

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To

The researchers of iodine deficiency disorder control programmes

Stellingen

1. A positive effect of iodine supplementation before and during pregnancy has been shown previously in studies in both humans and animals. For the first time, a strong positive effect on mental development of supplementing children with iodine has been demonstrated (this thesis).

2. Iodine supplementation seem to have a more positive effect than iron supplementation in improving mental development in children (this thesis).

3. Supplementation with iodine and iron stimulates mental development more than somatic development in children (this thesis).

4. An oral dose of 1mL Lipiodol UF (490 mg of I) was found to be inadequate to provide a regular supply of iodine for one year (this thesis).

5. The desire to obtain a second blood sample from each child jeopardized the completion of the study thus illustrating that local traditions, beliefs and organizations play a significant role in the success and failure of scientific studies in traditional societies (this thesis).

6. Although iodine is essential for fetal development and growth, there are other essential factors which should not be forgotten once a child is born (this thesis).

7. For the economic maladies of developing countries, an honest dictator may prove to be better than a democrat with a price-tag.

8. The technology of iodinating salt is simple but getting iodinated salt to those who require it is not as simple as it appears.

9. Recent political change in the second and the third world have given to many people the false impression that market economies are expressways to prosperity and that democracy is synonymous with doing what you want.

10. The ethnic conflict in the Balkans, the tribal conflicts in Africa, and various territorial conflicts in Asia and Latin America are vivid examples of the risks that still dominate the future of *Homo sapiens.*

11. Is it not time we stop manipulating nature?

12. If the world is to be recreated I pray to God that he will make all countries into separate islands!

Stellingen behorende bij het proefschrift "Effect of iodine and iron supplementation on physical, psychomotor and mental development in primary school children in Malawi" van Ramesh M. Shrestha, Landbouwuniversiteit Wageningen, 14 juni 1994

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PREFACE

Since I joined UNICEF in 1982 and became involved in iodine deficiency disorders (IDD) control programmes in Nepal, I have been impressed by the magnitude of the IDD problem globally. I had some very frustrating years while working in a UNICEF-funded salt iodization programme in Nepal but that did not diminish my interest in the subject of IDD. I was also involved in organizing the inaugural meeting of ICCIDD in Kathmandu in 1986 which broadened my horizons and contacts with IDD experts. In 1986 I was assigned to UNICEF Malawi where my interest in IDD continued, especially on the social and economic aspects. It was not easy to focus on one area while my job required my attention on many other areas of high priority such as immunization and primary health care.

It was in 1989 that I met Professor Hautvast, Professor Clive West and Dr Frits van der Haar during the African Nutrition Congress in Harare where I discussed the possibility of doing this research. I would like to thank Professor Hautvast for accepting me as a PhD fellow in the Department of Human Nutrition, Wageningen Agricultural University. I would like to thank Clive for his support from the very beginning of this study in designing the study, field operation and preparation of various papers. I would also like to than Dr Frits van der Haar for his ideas on this research. Thanks are also due to Mrs Grietje van der Zee for all assistance while I was in the field and in the Department.

The idea of this research was fully supported and encouraged by Mr Ken Williams, who was then the UNICEF Representative in Malawi. I highly appreciate his support throughout. I would also like thank Dr Peter Greaves, former Senior Advisor on Micronutrients, UNICEF New York for financial support to complete the baseline field work. Soon after the baseline data collection was completed I had an opportunity to work in Vietnam. This would mean starting arrangements for revisiting Malawi to complete the final tests. I would like to thank Mr Tarique Farooqui, then UNICEF Representative to Vietnam for his support to complete the field work. After completing the data collection I was able to breathe and carry on with data cleaning and analysis and drafting papers in my spare time. Early in 1992 Mr Stephen Woodhouse replaced Mr Farooqui in UNICEF Vietnam as the new Representative. He had been the Chief of Training Division in UNICEF New York. His firm belief that UNICEF needs members of staff, who are a mixture of academic and programme implementer, was to my advantage. I would like to thank him very much for his encouragement and allowing me to take my accumulated leave which enabled me to be in Wageningen to complete the writing of this thesis.

The Government of Malawi, with UNICEF support, was in the process of distributing iodized oil capsules in several iodine-deficient districts. This gave me a unique opportunity of doing this study with minimum administrative difficulties. The Ministry of

Health of the Government of Malawi recommended Ntcheu district as an appropriate site. I would also like to thank Professor P.R. Khonje of the Health Science Research Committee and the Medical Ethics Committee for his support and assistance. I also owe my thanks to Mrs. Lilian Selenje, Nutritionist of the Ministry of Health for her contribution to designing the study. The Assistant District Education Officer in Ntcheu District Mr Ntakati provided the necessary support in obtaining local school lists, student lists and helped in introducing the research team to the selected schools. I sincerely thank him for his efforts. I would like to thank Mr Alister Ager, Lecturer in the Department of Psychology, Chancellor College, University of Malawi for training the field workers. His assistance in this work was crucial. The assistance of Dr Peter van Maren, District Medical Officer of Ntcheu District who allowed me to use the pathology laboratory for various purposes was invaluable.

Professor Nico Bleichrodt from the Department of Work and Industrial Psychology, Free University of Amsterdam eagerly contributed in selection of various test materials. I would like to thank him also for lending the tapping test equipment and reviewing various papers. The test of reaction time not only required specialized skills but also required specialized equipment which was generously lent by Dr Fons van de Vijver, Department of Social Sciences, Tilburg University. I would like to thank him for the equipment and his assistance in reviewing the data. I would also like thank Ms Janneke Mess and Ms Ellen de Jong, graduate psychology students from Tilburg University, for administering the reaction time test.

One of the tests selected for the present study was the lung function of children which required skilled test administrators. I would like to thank Mr Patrick Booms and Ms Suzanne Verver, biomedical research students from the University of Leiden for their assistance in implementing this test and Professor J.P. Vandenbroucke of the Department of Clinical Epidemiology and Professor Ph.H. Quanjer of the Department of Physiology, both of the University of Leiden for useful discussions on the data. Patrick and Suzanne received financial support from WSO (Stichting Wetenschappelijke Studiereizen Ontwikkelingslanden).

Two additional PhD fellows from Wageningen, Ir Inge Brouwer and Drs Carina Furnée also came to Malawi to carry out nutrition research. Throughout the period of the field work Inge and Carina provided much needed inspiration and humour. I highly appreciate their insights and assistance during the field operation. During the period of three years, more than 10 students from Wageningen, attached to one of the three projects came to Ntcheu for completing practical work. Thus, Ntcheu became a mini research station of the Department of Human Nutrition for a while!

I would also like to thank Thrasher Research Foundation and their Assistant Director Dr Robert Briem for additional funds for this field work and analysis of data. I also owe by debt to Guerbet Laboratories, France for supplying Lipiodol® and its placebo for use in the field. The analysis of urine sample were done in the Department of Animal Physiology, Wageningen Agricultural University. I would like to thank Professor Daan van der Heide, Mr Theo Viets and Ms Jannie Bos for the timely analysis of all urine samples.

Finally I would like to thank the three headmasters, field assistants and children of Lizulu, Mlanda and Chirobwe primary schools without whose patience and support I would not have been able to conduct the field work which formed the basis for this study.

Wageningen February, 1994

CHAPTER 1

Introduction

Appreciable improvement in life expectancy and food production has been achieved worldwide but the prevalence of malnutrition in children under five years of age is on the increase. In addition there are over 2 billion people, located primarily in Asia, Africa, Latin America and the Caribbean, deficient in one or more micronutrients: babies continue to be born mentally retarded as a result of iodine deficiency; children go blind and die young due to vitamin A deficiency; and a high proportion of women and children are adversely affected by iron deficiency. These are nutrients which are essential for life: the vitamins and trace elements which affect learning, productivity, health and survival itself (1). They cannot be synthesized in the human body but must be provided in the diet. The amounts required are small - micrograms or milligrams - hence the term micronutrient (2). The accurate assessment of micronutrient deficiencies is difficult because they are not overtly evident in affected populations. Hence the term *hidden hunger* was coined by the sponsors of the micronutrient malnutrition symposium in 1991 (2). With this background knowledge, Ministers and Plenipotentiaries representing 159 states recently declared their intention to eliminate hunger and all forms of malnutrition giving particular attention to micronutrient malnutrition (3).

It is now realized that prevention and treatment of micronutrient deficiencies is possible at a reasonable cost (2). While efforts to increase production of adequate food are important for feeding the growing world population, normal intellectual and physical development associated with micronutrient sufficiency calls for as much resolution if the potential of five billion human beings is to be fully realized. Apart from the three micronutrients most often lacking in the diet - vitamin A, iodine and iron - other micronutrients such as selenium and zinc are receiving increased attention but their exact role and impact when deficient are not yet clearly understood. Therefore priority is being given to controlling deficiencies of vitamin A, iron and iodine to achieve the goals of human development (4).

Prevalence of micronutrient deficiencies

Of the 2 billion people worldwide at risk of micronutrient malnutrition (1), at least one billion individuals show clinical signs of deficiency such as blindness, mild to severe mental retardation, deaf mutism, goiter, anaemia, weakness and general lethargy. The deficiencies are almost invariably found against a background of protein-energy malnutrition (1). The magnitude and extent of micronutrient malnutrition vary from nutrient to nutrient and country to country. Iodine deficiency depends on the content of iodine in soil and water. Crops grown in iodine-deficient soils almost invariably lack iodine, hence human beings and animals living on crops produced in these areas will also be iodine deficient.

Inorganic iron on the other-hand is available widely all over the world in legumes, cereals and vegetables. However only about 5% of inorganic (non-heme) iron is absorbed by the human body. Heme iron, which is found in meat and poultry products, is readily absorbed but is often consumed in small amounts because of the high cost of meat and poultry products especially in developing countries. It also has the advantage that it stimulates the absorption of non-haem iron. Other factors which can increase the absorption of iron, sometimes up to a factor of 10, are increased acidity of foods and increased consumption of foods rich in vitamin C. Conversely other substances in foods, such as phytates and polyphenols present in many plant foods, can inhibit absorption of inorganic iron. Those at risk generally lack the necessary knowledge to formulate their diets appropriately but often they do not have the necessary resources. In addition in many societies, food taboos prevent the consumption of red meat.

Vitamin A and over 600 different carotenoids are found in fruits, vegetables, fish, egg, meat, poultry and dairy products (5). WHO/FAO recommends a daily intake of 600 μg retinol equivalents for adult males with less for children and non-pregnant non-lactating adult women and more for pregnant and lactating women. Deficiency of vitamin A results in serious visual impairment, high rates of morbidity and mortality in children. WHO estimates that 6-7 million cases of xerophthalmia occur annually, of whom about 10% of cases exhibit serious corneal damage. An additional 20-40 million suffer from mild deficiency (6). Over the past few years the whole emphasis of research into vitamin A deficiency has shifted from xerophthalmia to child survival. Epidemiological studies have shown an increased risk of morbidity and mortality from respiratory and gastrointestinal diseases in children deficient in vitamin A. Supplementation with vitamin A to children deficient in vitamin A has shown a mean reduction in mortality of 23% (7). The intake of vitamin A is inadequate due to seasonality of food sources, early weaning from breast-milk, and practices which limit the provision of vitamin A-rich foods to children. Dosing with 200,000 IU of vitamin A (60 mg retinol) for children over the age of one year with half the dose for younger children is recommended for combatting the problem in the short term but there is no doubt that a food approach is required in the long term in order to improve the intake of vitamin A (8).

A brief review of the two micronutrients discussed in this thesis, iodine and iron, and their manifestations are presented below. Since deficiencies of both these micronutrients are very common, they often overlap. Both affect physical and mental ability of individuals.

Iodine in the human body

The healthy human adult body contains 15 - 20 mg of iodine of which 70 to 80% is stored in the thyroid gland which weighs only 15 to 25 g highlighting the importance of the thyroid gland in the overall metabolism of iodine (9). Humans need to consume 100 to 150 μg of iodine daily from food. Of this amount the thyroid gland uses about 60 μg of iodine each day to maintain an adequate supply of thyroxine (T4) and triiodothyronine (T3) required for various body functions. The level of T4 and T3 in blood can be used as an indirect measure of iodine status in individuals.

Manifestations of Iodine Deficiency Disorders

The most apparent manifestation of iodine deficiency is goiter, an enlargement of the thyroid gland but the spectrum of disease associated with iodine deficiency is much greater. The term iodine deficiency disorders (IDD) refers to this entire spectrum of iodine deficiency (10) and includes stillbirths, abortions, endemic cretinism, and a wide range of physical and mental anomalies while, although less obvious, have serious consequences (11,12). Hence iodine deficiency, in terms of its effect on mental function, is not an all-or-none phenomenon but rather a condition that exposes human individuals, outwardly normal looking to varying degrees of physical and mental retardation. This makes iodine deficiency a disease of entire populations and not just of individuals. The various consequences of IDD can be summarized as follows:

Goiter

The normal thyroid gland of human beings is equal in size to the terminal phalanx of the thumb. A person is regarded as having goiter when the thyroid gland is enlarged to such an extent that the lateral lobe is bigger than the terminal phalanx of the individual being examined. A goiter of this size is not visible but can be palpated. When the thyroid gland is further enlarged, it becomes visible and it is estimated that over 200 million individuals mostly in developing countries have visible goiter (9). The pituitary gland of individuals with iodine deficiency produces additional thyroid stimulating hormone which intensifies the enlargement and subsequent proliferation of thyroid cells. Thus the hypertrophy and hyperplasia of the thyroid gland is responsible for the development of goiter. The prevalence and severity of goiter increases with increase in severity of iodine deficiency, and becomes almost universal in populations where iodine intake is less than 10 μg per day (9). Large goiters sometimes develop nodules which can exert undue pressure on the trachea and esophagus thus causing difficulty with breathing and swallowing.

Hypothyroidism

This is a state in which the body does not produce enough thyroid hormone and results in physical and mental lethargy (13). The most common cause of hypothyroidism is iodine deficiency although one child in 3,000 can be born with congenital hypothyroidism. Regardless of its cause, in children it can result in mental and physical retardation and, if severe, lead to cretinism. In babies and young children, hypothyroidism can be detected by elevated serum levels of TSH while in older children and adults, in whom the thyroid has become autonomous of the hypothalamus-pituitary axis, it can be detected by reduced levels of T4 in serum.

Cretinism

Cretinism occurs when the supply of T4 to the developing fetus is inadequate. Initially T4 is supplied by the mother but later, the fetus is capable of synthesizing T4 itself. The term cretinism has been used to define two unrelated conditions: endemic cretinism which is associated with goiter and iodine deficiency, and sporadic cretinism which is related to congenital hypothyroidism and not to endemicity of IDD. Cretinism associated with iodine deficiency was first described by McCarrison in 1908 (14). After a series of clinical examinations, he was able to classify cretinism into two types: nervous and myxedematous. The nervous type of cretinism was characterized by mental defects, deaf mutism, occasional squint, spastic diplegia and a spastic rigidity affecting legs and stature. Myxedematous cretins exhibited retarded physical growth, dry and coarse skin, apathy and mental deficiency. Additional features of myxedematous cretinism were later described by several authors and include retarded musculo-skeletal growth, weak abdominal muscles, inadequate bowel function and delayed reflexes. The features of myxedematous cretinism are similar to those of sporadic cretinism arising from the complete lack of a thyroid gland or congenital defects in the functioning of the gland resulting in impaired thyroid hormone synthesis. Both nervous and myxedematous cretinism can be found in a common geographic area with some cretins having features of both. In general, mental deficiency is not so severe and deaf mutism less common in myxedematous cretinism compared with neurologic cretinism. Frequently iodine deficiency produces delays in intellectual and physical developmental insufficient to be classified as cretinism, a condition which has been described by some authors as sub-cretinism while others refer to iodine deficiency development retardation (4).

Reproductive failure

Women living in severe iodine-deficient areas have an increased risk of abortions, miscarriages and still births (15). Although estimates have been made, the extent to which this risk can be attributed to iodine deficiency is yet to be established. Studies reported from Zaire (16) have shown that women supplemented with iodine during pregnancy delivered heavier babies who also showed higher rates of survival compared to children born to unsupplemented women. Similar findings were also reported from a study from Papua New Guinea (17). Thus the available clinical and epidemiological evidence suggests that iodine-deficient communities are at increased risk of reproductive failure causing reduced fertility, increased abortions and stillbirths, impairment of structural and functional development of the fetus resulting in increased risk of congenital anomalies in infants born at term to hypothyroid mothers (18).

Psychomotor and mental development

The results of studies on iodized-oil trials in Papua New Guinea and Ecuador during the late 1960s firmly established the fact that cretinism can be prevented by supplementation with iodine before or during early pregnancy. Recently questions were being asked whether iodine deficiency also affects mental well-being of individuals who are not cretins but deficient in iodine. Results of psychomotor and mental development tests conducted in children born to mothers treated with iodine during different stages of pregnancy clearly indicate that children born to iodine-deficient mothers and children who did not receive iodine during early fetal period perform less well in various scales of psychomotor and mental development tasks. This led to the suspicion that mental performance of individuals living in an iodine-deficient environment could be subnormal. This suspicion was confirmed by studies from China, Indonesia, Ecuador, Chile, Bolivia and Spain. Can the consequences of such deficiencies be corrected by supplementation with iodine? Few studies have shown improvement in psychomotor functions while mental performance remained unchanged. Several studies have demonstrated improvement in both psychomotor and mental performance but were statistically not significant. The overall view is that correction of iodine deficiency improves both psychomotor and mental performance but how much is improved remains unclear. The answer to this question probably depends upon the extent of deficiency, duration of exposure and age at exposure.

Economic Implications of IDD

The productivity of populations depends upon the physical and mental capacity of the individuals in the population. Since it has been shown that lack of iodine during pregnancy of mothers results in slower physical and mental development of children (12), individuals born of iodine-deficient mothers are less productive and hence a burden on society. In addition, mental retardation increases difficulty in learning resulting in a waste of education resources which are scarce especially in developing countries. Not only is the human population affected, so is the animal population (10). Iodine deficiency results in lower reproductive performance, lower weight at birth and at maturity, and low production of meat, milk and wool in farm animals (9). All of these effects on animals have serious economic implications.

Iron in the human body

Much is known about iron from a technological and biological point of view (19,20) yet deficiency is one of the most common nutritional problems worldwide (21). The average adult male contains about 3.8 g of iron while there is about 2.3 g of iron in the average adult female. Iron-containing compounds in the human body can be classified into three categories: those with metabolic activity, those for storage and those for transport. About 85% of non-storage iron is found in haemoglobin while 5% is found in myoglobin in muscle and 10% elsewhere including intracellular heme enzymes involved in oxidative metabolism. The proportion of total iron in storage compounds mainly in liver and bone marrow, varies widely and averages about 25% in men and 12% in women. Iron absorption is regulated by the amount of iron in body stores. In iron-deficient individuals, iron stores may be almost entirely depleted before signs of iron-deficiency anemia develop while conversely, tissue damage usually does not occur until there is a 20-fold increase in iron stores.

Manifestation of iron deficiency

Manifestations of iron-deficiency anemia are usually subtle although they can lead to death in extreme cases. Among the effects of iron deficiency are impaired work performance and retarded cognitive development.

Iron and physical work performance

Studies in humans and laboratory animals have shown that anemia causes a substantial reduction in work capacity which becomes particularly evident when the concentration of haemoglobin falls below 100 g/L (21). The practical implications of these conditions have been demonstrated in studies in Indonesia (22), Sri Lanka (23) and China (24). In the Indonesian study, anemic men in rubber plantation were found to be much less productive than men with normal haemoglobin levels. In the study in Sri Lanka, both men and women with lower haemoglobin levels working on tea estates were found to be less productive than those with normal haemoglobin levels. In both studies, iron supplementation was able to improve the work performance with the greatest improvements being noted among those who had the lowest haemoglobin levels at the start of the study. In the Chinese study (24), 12 weeks after supplementation with iron, productivity of iron-supplemented anemic female cotton-mill workers had increased by 18% compared to non-treated anemic workers. Productivity was measured in terms of the amount of yarn produced per day.

Iron and cognitive development
There is increasing evidence that psychomotor development and intellectual performance are impaired by iron deficiency (25). Studies on iron-deficient infants and toddlers have shown that sensory development, fine and gross motor development, and language development (26,27) are retarded compared with children with normal iron status. In a matched group of anemic and non-anemic children aged 3 to 6 years, the performance of anemic children in tests of discrimination and learning was less than that of non-anemic children. Three months of oral supplementation with iron brought their scores close to those of the non-anemic children (28). In several related studies (29-36), iron supplementation was also shown to have a positive effect on improving various cognitive skills in preschool and primary school children. In one large study in Thailand (34), anemic children had lower IQ scores and lower school achievement than non-anemic children at the beginning of the study. After 10 weeks of supplementation with either iron or placebo, all children improved their IQ while the previously anaemic children who were treated with iron improved their language and mathematics score more than their non-anemic counterparts.

All studies, both those in developing and in developed countries, have illustrated a remarkable consistency in their findings (29). Iron-deficiency anemia has been found to be associated with poor performance in infant development scales, IQ and learning tasks in preschool children, and in educational achievement in school children. Such poor performance can, at least in part, be reversed with iron supplementation.

Magnitude of the problem and what can be done?

Deficiencies of the three micronutrients, vitamin A, iron and iodine, have a devastating impact on societies particularly those in developing countries. The World Bank (1) has estimated that the direct annual cost to a developing country with a population of 50 million, similar to countries in South Asia with respect to deficiencies of the three micronutrients, would be the loss of about 350,000 student-years due to learning difficulties, the loss of 1.3 million person-years of work, 20,000 preventable deaths, and 11,000 children severely handicapped due to cretinism or blindness.

Most nutrition programmes in developing countries are more concerned with the supply of adequate energy and preventing physical growth failure than with controlling micronutrient malnutrition. Since the causes of micronutrient malnutrition are food related, it might be expected that national development which addresses the problem of food supply would also take care of the problems of micronutrient malnutrition. However, iodine deficiency cannot be combatted through an agricultural or food approach which does not involve fortification and the development policies of most developing countries do not

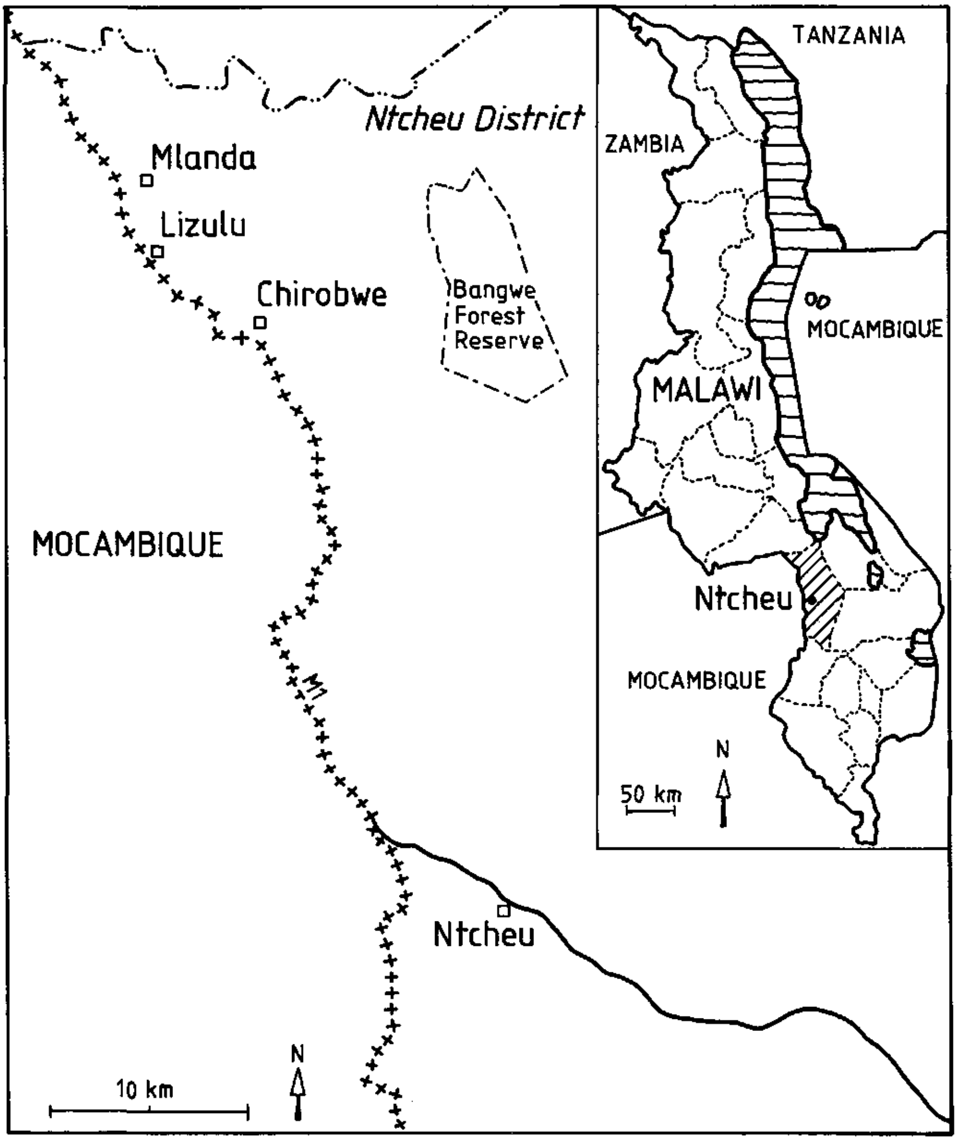

Figure 1
Map of Malawi and Ntcheu district showing the location of the district headquarters (Ntcheu) and the three schools in the north of the district where the studies were carried out.

address the specific issues of iron and vitamin A malnutrition. Policies are generally directed to the production of food for export. In addition, increased income and satisfying hunger do not necessarily lead to increased micronutrient intake.

Therefore it is essential that the problems of micronutrient malnutrition are addressed in many aspects of policy. For agro-industry, this means appropriate policies for regulating production of selected crops and processed foods, pricing and marketing. Although there are a number of basic scientific questions yet to be addressed, the biggest barrier to alleviating the problems of micronutrient malnutrition are the lack of political will and the allocation of sufficient resources.

In 1990, 1991 and 1992, there was a series of three international conferences which proposed that the global problems of micronutrient malnutrition should be addressed seriously (2-4). It was decided that deficiencies of vitamin A and of iodine should be virtually eliminated before the turn of the century and iron-deficiency anemia in women of child-bearing age should be reduced by one third in the same period. UNICEF regards the problems as being more urgent and has set the goals at eliminating vitamin A and iodine deficiencies by the end of 1995 which is less than two years away. Thus there is mounting pressure to take the problems of micronutrient malnutrition seriously.

Present Study

Objective

The objective of the present study was to evaluate the effects of iodine and iron supplementation on physical, psychomotor and mental development of rural primary school children in Malawi.

Study area and population

The study was conducted in the Republic of Malawi (Figure 1). Malawi is a land-locked country situated in south-central Africa between Tanzania to the north and east, Zambia to the west and Mozambique to the south and east. It is about 850 km long and 80 to 160 km wide. The altitude in Malawi is very variable. The lowest land is along the Shire valley in the south which is about 50 to 100 m above sea level. In the Lake Malawi basin, the altitude varies between 500 and 700 m while the Nikya plateau in the north and the Mulanje mountains in the South reach up to 3000 m above sea level. Lake Malawi is the third largest lake in Africa having an area of about 24,000 sq km.

Administratively, the country is divided into three regions and 24 districts. Based on the national census in 1987 (36), the population of Malawi in 1990 was estimated to be

8.2 million people not including the Mozambican refugees. The country is predominantly rural with about 90% of the population depending on agriculture for their livelihood. The main food crop in Malawi is maize which is predominantly for local consumption while the principal cash crops are tobacco, coffee, tea and sugar cane which provide about 80% of export earnings.

Education system in Malawi

The aim of the Government of Malawi is to achieve Universal Primary Education (UPE) while the national development policy (37) regards education as fundamental to national development. The majority of schools are funded by the Central Government while some schools are funded by local authorities and missions.

The school year runs from October to August. Primary school education lasts eight years divided into two phases: junior primary school from Standard 1 to Standard 5 and senior primary school from Standard 6 to Standard 8. The official age at entry into primary school is six years and children are expected to complete full primary school by the age of 14 years. The medium of instruction is Chechewa in Standards 1 to 4, Chechewa and English in Standard 5, and English only in senior primary school and higher institutions. Since only about 15% of primary school leavers enter secondary school, the primary school curriculum is adapted to make it relevant to the needs of rural population by introducing agricultural techniques, home economics, and handicrafts (38).

The present study was conducted in Ntcheu district of Malawi. It is located 170 km south of Lilongwe, the administrative capital of Malawi and 185 km north of Blantyre the commercial capital of Malawi. Ntcheu is inhabited by about 210,000 individuals of whom 46% are children under 15 years of age (39). This district is known to fall in the iodine-deficiency belt of Malawi (40). With respect to micronutrient malnutrition, Malawi can be regarded as typical of many developing countries not only in Africa but also elsewhere in the world. The extent of micronutrient deficiencies, the lack of micronutrients in the diet, the problems with salt iodination, and the difficulties in reaching the poor are all too familiar in developing countries. Thus the findings of the present study in Malawi will be of interest not only to Malawi but also to many other developing countries.

Outline of the Work

The research comprised three phases.

Phase One

This phase, from May to September 1990, consisted of the formation of a study team with full participation of the Ministry of Health of the Republic of Malawi, particularly the Nutrition Section. A double-blind placebo-controlled 2x2 design with iodine and iron treatments was selected for this study. The protocol of the proposed study was approved by the Medical Ethics Committees of the National Research Council of the Office of the President and Cabinet in Malawi and of Wageningen Agricultural University. Then three schools along the Ntcheu-Dedza district border were selected for the study in conjunction with the Ministry of Education and District Education Officer. The study team met with the district education authorities and discussed in detail the concept and purpose of this study. This procedure was repeated with the school headmasters and the local school committees.

Six local secondary school graduates were selected as interviewers. They all belonged to the same ethnic group and spoke the local language of the area, Chechewa, which was spoken by the subjects. The interviewers were briefed on the purpose of the study and were trained in various aspects of field work including anthropometry and interviewing techniques by the author and a psychologist from Chancellor College of the University of Malawi in Zomba. This was followed by a pretest in a village, 27 km away from the study area. Each interviewer interviewed a minimum of ten children during the pretest during which time no major problems were encountered.

Phase Two

Phase Two started as soon as the 1990 school year commenced (first Monday of October 1990) and continued until July 1991. A list of all children enrolled in Standards One and Two were obtained from the school register. All children born between January 1982 and December 1984 were selected and stratified by age, sex and class for each school. Four children from each strata were chosen at a time and randomly allocated to each of the four groups. After allocation of children to groups, each group of children was allocated randomly to one of four treatment regimes. A series of tests was conducted as indicated in the flow-chart (Figure 2). After the tests, each child was given the assigned combination of treatment regime: a single dose of iodized oil (Lipiodol® UF, 1 mL, 490 mg I) or a placebo of poppyseed oil together with iron tablets (200 mg ferrous sulphate, 60 mg Fe) or placebo each weekday during school term. The parents of each child participating in the study were interviewed to gather basic socio-economic information. Three months after supplementation, a second urine sample was obtained from each child to monitor urinary iodine excretion and the tapping test was carried out to determine whether the functions measured by this parameter were influenced at this stage.

Phase Three

Phase Three was in the period October-November 1991 during which time a second round of tests were carried out using the same test methods, the same questionnaires and the same interviewers in the same class-rooms as in Phase Two.

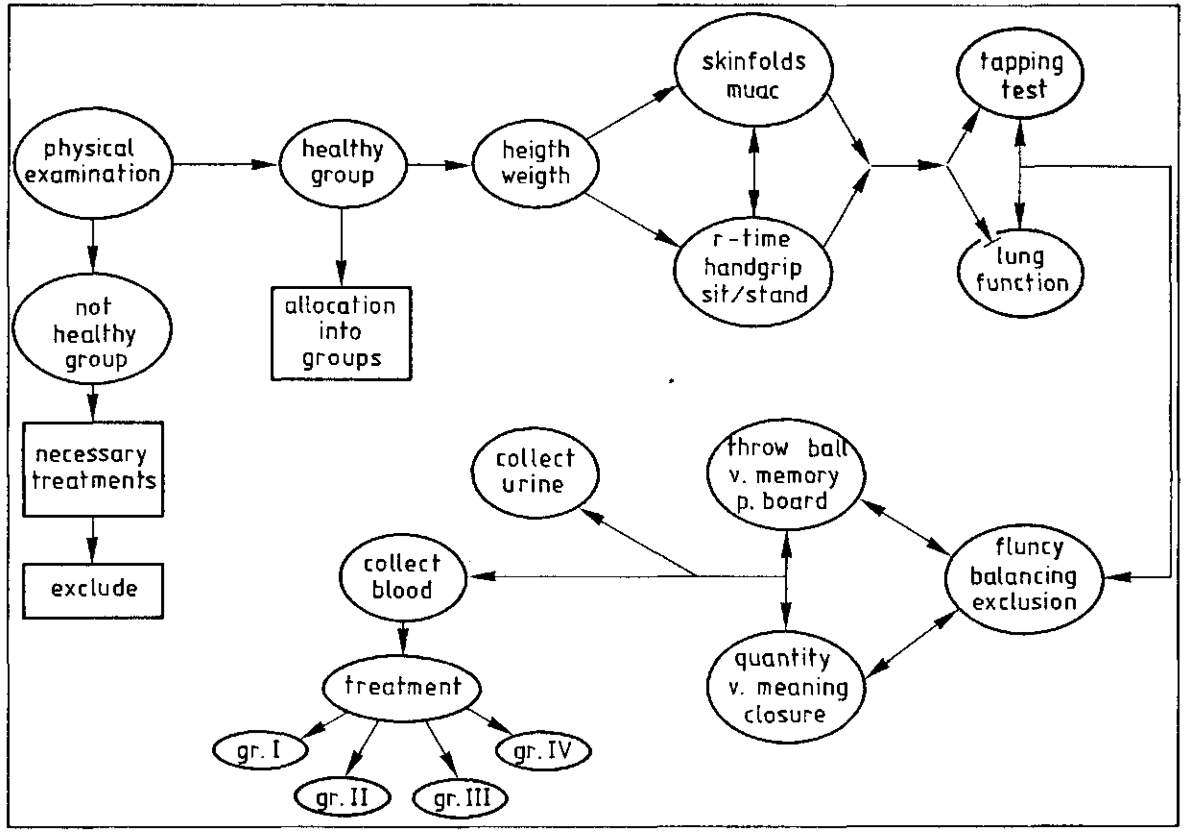

Figure 2
Flowchart of activities in Phase Two and Three of the study

Conduct of the field work

The selection of schools, selection of field workers and their training all went smoothly. The team was able to collect baseline urine and blood samples as planned in order to establish baseline parameters of iodine and iron nutriture. All baseline anthropometric measurements and tests of mental and psychological development were also conducted smoothly. The procedures for the administration of supplements presented no problems. Collection of urine and administration of the tapping test 3 mo after supplementation went according to plan.

During Phase Three, severe objections were made by children and their parents to providing blood samples with all children from the schools involved beginning to fear the study team including the Malawian field workers. As this threatened to jeopardize the entire study, the plan to collect further blood samples designed to provide information on iron status was abandoned. Thus the dropout from the study was due primarily to children who had left school for other reasons. Collection of urine and administration of the tests in Phase Three then went according to plan.

Outline of thesis

The following four chapters in this thesis describe the results of the present study and an overview of the previous work done in the field of iodine deficiency disorders in relation to mental development of children. Chapter 2 deals with the main findings of the present research with respect to the physical and psychomotor development. Chapter 3 presents the findings related to mental development. Chapter 4 presents an overview of work conducted on the relationship between iodine deficiency and mental and psychomotor development. In Chapter 5, the results of work carried out on lung function with respect to indices of FEV_1 and FVC during the present study are presented while Chapter 6 is a general discussion and includes the main conclusions and some recommendations. The thesis concludes with a brief summary both in English and Dutch and a curriculum vitae of the author.

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CHAPTER 2

Supplementation with iodine and iron improves selected parameters of physical stamina and psychomotor development in Malawian children

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(submitted for publication)

Summary

A double-blind placebo-controlled study involving oral dosing with iodized oil and iron was carried out in primary school children aged 6 - 8 yr in Ntcheu District, Malawi in order to investigate the effect of supplementation with iodine and iron on physical and psychomotor development. About 86% of children were at least moderately iodine deficient with urinary iodine concentrations below 0.4 μmol/L and 18% were anemic (blood haemoglobin concentration <110 g/L). Anthropometric measurements were made and physical and psychomotor tests were administered individually before and 10 mo after supplementation began. For the measurements of physical and psychomotor development, data were available on 241 to 321 subjects. Neither iron nor iodine supplementation had any effect on height, weight gain, body equilibrium or lung function. Iodine supplementation improved physical stamina as measured by handgrip ($p<0.01$) and intermittent sitting and standing ability ($p<0.001$); and eye-hand coordination ($p<0.01$) as measured by throwing balls into a box. Supplementation with iron improved eye-hand coordination ($p<0.01$).

Introduction

Deficiencies of iodine (1) and iron (2) are widely found in almost all developing countries. Both can limit a variety of body functions, depending on the severity of deficiency. In areas with severe endemic goiter, many individuals exhibit irreversible anomalies of intellectual and physical development (3) but it is apparent that a continuous spectrum of intellectual, nervous, physical and hormonal abnormalities may be seen even where the deficiency is not severe (4). Hetzel and Potter (5) were able to demonstrate that sheep fetuses in iodine-deficient mothers were considerably lighter in body weight and brain weight, and were different in physical appearance compared to fetuses conceived in iodine-sufficient sheep. The condition was reversed by introducing an iodine supplement before the third trimester of gestation. However, for maximum psychomotor and mental development, studies from Ecuador would suggest that adequate iodine nutriture in the first trimester of pregnancy is necessary for maximum mental and possibly psychomotor development (4). Thus the fundamental question is: to what extent, if any, can such negative effects be reversed in human beings after birth?

The functional implications of iron deficiency have also been documented (2,6). One of the most common negative effects of iron deficiency is reduced physical capacity as demonstrated by low work productivity in adults (7) and reduced cognitive development in children (8). The studies in Thailand (9), Indonesia (10), and Costa Rica (11) have shown that iron supplementation can, to varying degrees, improve the mental and psychomotor performance of children suffering from iron-deficiency anemia.

Malawi is an agricultural country in south-central Africa with a land area of 96,000 sq km and a population of about 7 million people (12). The education and administrative systems in Malawi are British in origin and have been maintained. Schooling in Malawi is neither free nor compulsory. Entry into primary school begins at age six but only about 60% of children have access to primary education. Goiter is known to be endemic in several districts in Malawi (13,14). In Ntcheu district, a visible goiter rate of 60% in the general population was reported in 1983 (13). No specific data on iron deficiency in children were available but data from MCH clinics (15) indicated that the prevalence of iron deficiency anemia in women was about 50% suggesting that anemia is a problem in children.

Since iodine and iron deficiencies often occur together, not only in Malawi but elsewhere, the manifestations of each deficiency are often difficult to unravel from one another although the mechanisms involved are different (8,16). However the main issue in question is to what extent the effects of each deficiency can be reversed. The purpose of the study reported here was to examine whether the physical and psychomotor development of children, living in a subsistence farming economy where iodine and iron deficiencies are endemic, can be positively influenced by supplementation with iodine and/or iron.

Subjects and methods

Study area

The study was carried out in the south-central African country of Malawi. The study area was in Ntcheu district, a combination of flat land and mountainous terrain, which is located 170 km south of the capital Lilongwe, and 185 km north of the commercial city Blantyre. Approximately 210,000 people, of whom 46% are children under 15 years of age, live in the district (12). The study population came from five villages in the north of Ntcheu district which is populated by subsistence farmers of the N'goni ethnic group. None of the villages were supplied with electricity or treated drinking water.

Subjects

Three Primary schools, about 9 km from one another, were selected and a complete list of all children admitted to Standards One and Two was obtained. All children (n=424) born between January 1982 to December 1984 were considered for enrolment in the study.

Study design

Several village committee meetings were organized through the local school committees to explain the aims and objectives of the study. Upon verbal approval of the parents, all children selected were medically examined for lung infection, hepatomegalia, splenomegalia, skin infections, pallor and xerophthalmia by a Senior Clinical Officer of Ntcheu District Hospital. No children were excluded on health grounds possibly because seriously sick children do not attend school. Several children with skin infections were treated. The children were stratified by class, age and sex for each school, and then four children from each category were selected at a time for random allocation to each of four groups. The groups were then randomly assigned to four different treatment regimes: placebo; iron; iodine; and iodine plus iron.

The study was double blind with the codes only being broken after the completion of the final test. For the groups not receiving iodine or iron, placebos identical in appearance and composition except for the active ingredient were provided. The iodized oil (Lipiodol UF®; 490 mg I/mL) and placebo (poppyseed oil) were provided by Guerbet Laboratories Ltd (Aulnay-sous-Bois, France) and the iron tablets (ferrous sulphate, 60 mg Fe) and corresponding placebos by Lomapharm Medicines (Rudolf Lohman, Emmerthal, GmHKG Germany). Iodized oil or poppyseed oil were provided as a single dose (1mL) administered orally with an Englass Swift® dispenser (The English Glass Company Limited, Leicester, England) in February 1991. One iron or placebo iron tablet was given to each child in the classrooms by the headmasters of the three schools each weekday during school term commencing in February 1991 until the completion of the final tests, with a break during the long vacation in August and September. The baseline anthropometric measurements were made and urine samples collected in October-November 1990; the baseline physical and psychomotor tests were performed in November-December 1990; and blood samples collected in January 1991. A second urine sample was taken from the children in April 1991. All measurements and tests, except collection of blood samples were repeated in October-November 1991. It was not possible to collect blood samples at this time because of opposition from the parents based on unfounded rumours. All tests were conducted between 8:00 and 12:00 during week days in classrooms made available by each school. The study was approved by the Medical Ethics Committees of the National Council for Medical Research of Malawi and the Department of Human Nutrition of Wageningen Agricultural University.

Somatic and biochemical indicators

Height, weight, mid-upper arm circumference (MUAC), triceps and biceps skinfolds were measured in duplicate, as outlined by WHO (17), by one of the authors (RMS) and trained field assistants. Results are expressed as the mean value and, if two measurements differed by a predetermined amount, they were repeated. Height was measured to the nearest mm (Microtoise) weight to the nearest 0.1 kg using an electronic scale (Tefal), skinfolds to the nearest mm by Harpenden callipers (Holtain, Wales) and MUAC to the nearest mm using a flexible steel tape. Urine samples were sent to the Department of Human and Animal Physiology of Wageningen Agricultural University where they were stored at -20°C prior to analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (18) adapted for use with a microtitre plate reader (Thermomax, Molecular Device Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with Softmax software provided by the manufacturer. All samples were assayed in duplicate and when measurements differed by more than 10% the analysis was repeated. The means of the measurements from each subject at each time point were used for analysis. A blood sample (5 mL) was obtained from the left forearm of all subjects for analysis of hemoglobin (Hemocue, Helsinborg, Sweden), hematocrit (microcentrifuge) and serum ferritin (kit supplied by Boehringer Mannheim GmbH, Germany).

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured by Printer Spirometer (Micro Medical Ltd. Chatham, Kent, U.K.). All children were instructed and demonstrated by a trained field worker and readings were taken by a graduate student only when the child demonstrated that the procedure was understood. Three readings were taken for each indicator and the scores were based on the highest values obtained for each parameter.

Physical stamina

All children were subjected to two tests of physical stamina: hand-grip and the sitting/standing test. A hand dynamometer (Jamar, Clifton, NJ, USA) was used to measure the hand muscle strength of both hands. Three measurements were made with each hand and the average of the six readings used. The sitting/standing test involves children sitting and standing as many times as they can in one minute, the time being recorded with a digital watch.

Psychomotor measurements

These comprised five indicators: pegboard (19), balancing (19), ball throwing (19), tapping board (19) and reaction/movement tasks (20) which are described briefly below. All times were measured with a digital stopwatch.

Pegboard test: This is a measure of speed and perseverance, and involved the child inserting pegs into holes of uniform size which form the outline of a butterfly in a thick transparent plastic board. The time taken for the child to insert the pegs into all the holes was recorded.

Balancing test: In this test, which is a measure of gross body equilibrium, the child was asked to stand on each foot without support for as long as possible with a maximum of 180 sec. The score was the mean time which a child could stand on each foot.

Ball throwing test: This is a measure of eye-hand coordination and involved throwing small balls into a box (46cm x 23cm x 25cm) 3 m away. Twenty golf balls were placed beside the child who was asked to pick up one ball at a time and throw it into the box. The number of balls which landed in the box (no time limit) was recorded as the score.

Tapping test: This test, which measures manual dexterity and accuracy, used a set of four rectangular metal plates of various lengths with regions electrically isolated from one another (Figure 1) and an electrode pen. The various regions of each plate, including hatched areas on each side, and the electrode pen were connected to a recording device which responded when the pen came in contact with each of the regions. Beginning with the shortest plate, a child was asked to tap the hatched regions on each side of the plate alternately beginning on the left, as many times as possible. The number of hits made in 10 sec was recorded automatically with hits on the plain surfaces being regarded as errors. The score was the sum of the correct number of hits on each of the four plates.

Reaction-time tasks: This set of tasks, which measures information processing time, was conducted using a computer-simulated programme. The equipment used comprised a TV monitor and a key-board used by the examiner and a second TV monitor and a response board (29cm x 35cm) with buttons (1.4cm x 1.4cm) used by the child (Figure 2). The number of buttons exposed on the response board could be altered by changing the cover of the panel. There was one simple reaction task (task A) and two choice reaction tasks (tasks B and C). Task A involved only two buttons. While pointing to the monitor screen, the examiner explained *'In a few moments, a small square will appear on the screen and you will hear a beep. And when you hear the beep and see the square you have to press this button* (the home-button at the bottom of the response board was indicated to the child). *After some time the square on the screen becomes black. As soon as you notice this, you should lift your finger from this home-button and press the other button at the top of the response board* (the top button was indicated to the child).

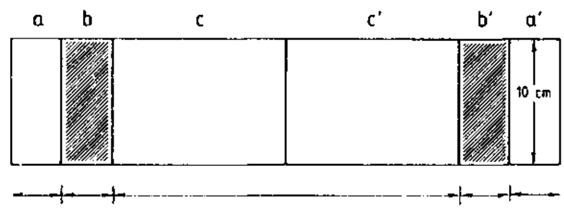

Figure 1
Diagram of tapping board. The width (cm) of a(a'), b(b') and c(c') were as follows: 2,2 and 2 on Board 1; 2,2 and 6 on Board 2; 4,4 and 12 on Board 3; 4,4 and 28 on Board 4

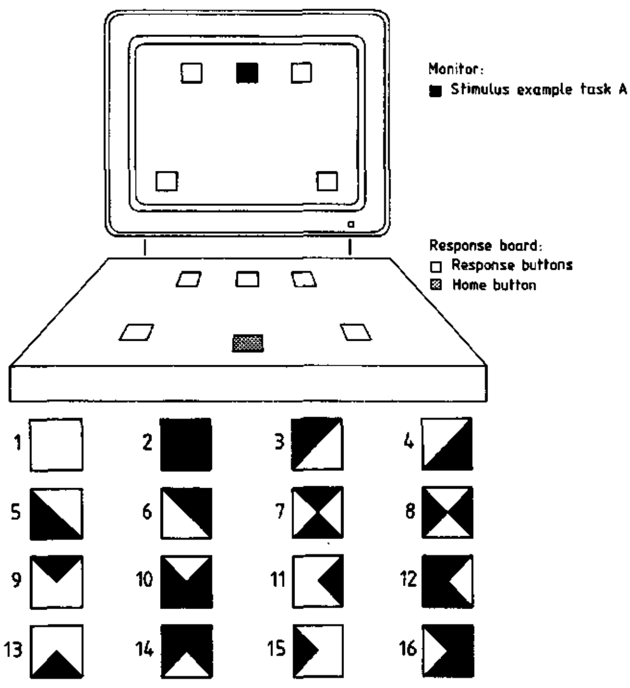

Figure 2
Diagram of: a, equipment for reaction time tasks showing monitor screen and response board, and b, stimulus patterns shown on monitor screen

After this explanation the child followed the procedure and, as soon as the child indicated that the procedure was understood, the task was carried out twice (Task A1 and Task A2). Tasks B and C each involved six buttons including one home-button on the response board. Both tasks sequences were similar to those in task A. Two geometric patterns were used in task B which were repeated (Task B1 and Task B2) while in task C there were 16 such patterns. For all these tasks, both reaction time and movement times were measured. Reaction time is defined as the interval from presentation of stimulus to lifting of the finger from the home button and movement time is defined as the interval between leaving the home button and pressing the response button.

Statistical analysis

Data were analyzed from those subjects for whom both measurements were available. The paired t-test was used to compare values between each time point while the two sample t-test was used for comparisons among various treatment groups both at baseline and for changes over the treatment period.

Results

There was no difference between the groups in household size, number of children per family, ownership of domestic animals (cattle and goats) and area of land owned by the families (Table 1). The mean age of children in each group was 7.1±0.8 yr. In addition, there was no difference between the groups in urinary iodine concentration, blood hemoglobin and hematocrit, and serum ferritin (Table 2). The urinary iodine concentration in the total population of 0.22±0.17 μmol/L (mean±SD) would indicate that the population was moderately iodine deficient (21). Examined in another way, of the total population studied, 52% had urinary iodine concentration <0.16 μmol/L (severe iodine deficiency); 34% had values 0.17 -0.40 μmol/L (moderate iodine deficiency); and 11% had values 0.41 - 0.79 μmol/L (mild iodine deficiency) (21).

Based on hemoglobin levels <110 g/L, 18% of the children can be classified as anemic while based on hematocrit <0.35, 16% are anemic. Iron stores, as determined by serum ferritin levels <20μg/L were depleted in 16% of the children. After 3 mo, urinary iodine concentration increased in the iodine and iodine plus iron groups from 0.15 (0.09, 0.25; median, 25th and 75th percentiles) μmol/L and 0.15 (0.08, 0.26) μmol/L to 0.42 (0.01, 1.19) μmol/L and 0.32 (0.11, 0.84) μmol/L respectively. After 11 mo, the median values had fallen to 0.18 (0.08, 0.50) and 0.16 (0.06, 0.34) μmol/L respectively. There was no significant change in the two groups which did not receive iodized oil. A change in hematological indices could not be examined because of objections from the community in drawing further blood samples.

Table 1 **Characteristics of the families of children participating in the study***

Family characteristics	Treatment groups			
	Placebo (n=72)	Iron (n=81)	Iodine (n=77)	Iodine & iron (n=78)
Children (n)	4.2±1.5	4.2±1.8	3.8±1.5	4.3±1.7
Household size (n)	8.0±2.7	7.6±2.7	7.7±2.7	7.8±2.6
Cattle and goats (n)	6.5±8.8	6.5±6.0	5.4±5.4	5.0±5.3
Land (ha)	0.76±0.45	0.72±0.50	1.04±0.60	0.76±0.50

* Mean±SD.
The total number of children in each group was 82, 81, 79 and 82 respectively.

Table 2 **Biochemical characteristics of subjects at baseline***

	Treatment groups				
	Placebo (n=72)	Iron (n=81)	Iodine (n=77)	Iodine (n=78)	Total & iron (n=308)
Urinary iodine	0.15	0.16	0.15	0.15	0.15
(μmol/L)	(0.09, 0.26)	(0.07, 0.30)	(0.09, 0.25)	(0.08, 0.26)	(0.08,0.27)
Hemoglobin	121	120	121	119	120
(g/L)	(117, 128)	110, 128)	(111, 127)	(114, 128)	(113, 128)
Hematocrit	0.38	0.38	0.37	0.38	0.38
	(0.36, 0.41)	(0.35, 0.40)	(0.25, 0.40)	(0.35, 0.40)	(0.35,0.40)
Serum ferritin	38.5	47.0	39.5	40.0	41.0
(μg/L)	(25.2, 63.2)	(27.0, 64.2)	(21.2, 75.5)	(24.2, 61.0)	(24.7,64.0)

* Median (25th, 75th percentile).
There were no differences between the four treatment groups in any of the parameters measured (Student's t-test).

Table 3 **Effect of iodine and iron supplementation on physical growth and lung function***

		Treatment groups			
		Placebo	Iron	Iodine	Iodine & iron
		(n=67)	(n=74)	(n=74)	(n=79)
Height (cm)	baseline	117.1±6.7	114.4±5.9	114.9±6.0	116.1±6.7
	final†	123.5±6.7	119.6±5.7	120.6±5.9	122.0±6.9
Weight (kg)	baseline	20.5±2.4	19.5±2.5	20.1±2.6	20.5±3.0
	final†	23.2±3.0	21.7±2.8	22.3±2.8	22.8±3.4
MUAC (cm)	baseline	16.8±1.1	16.5±1.1	16.8±1.1	16.8±1.2
	final	17.0±1.1	16.9±1.3	17.1±1.4	17.0±1.2
Sum of four skinfolds (mm)	baseline	20.3±4.9	20.4±5.9	19.5±4.7	19.8±3.9
	final	19.0±4.0	18.5±4.1	19.9±3.4	19.0±3.7
Upper arm muscle area (mm^2)‡	baseline	1785±250	1772±269	1872±335	1779±243
	final†	1944±265	1881±276	1940±253	1974±287
Upper arm fat area (mm^2)‡	baseline	509±126	501±144	495±140	491±116
	final	517±138	501±138	488±123	512±128
		(n=76)	(n=73)	(n=74)	(n-63)
FEV_1 (L)	baseline	1.02±0.22	0.93±0.19	0.99±0.23	0.97±0.22
	final	1.20±0.24	1.11±0.23	1.14±0.23	1.16±0.24
FVC (L)	baseline	1.15±0.30	1.04±0.23	1.12±0.32	1.35±0.29
	final	1.45±0.32	1.31±0.26	1.38±0.29	1.39±0.30

* Mean±SD.

† The means of height, weight, and upper arm muscle area over the treatment period were statistically significant using paired t-test ($p<0.001$).

‡ For method of calculation see references 23 and 24.

Physical growth and lung function

Comparisons not related to treatment: The anthropometric characteristics of children and lung function (Table 3) in the four treatment groups were similar at the beginning of the study. Overall 2% were wasted and 27% were stunted (17). This observation confirms the high prevalence of stunting in Malawi reported previously (22). Height and weight showed a considerable increase after the intervention in all four groups but there were no changes in the sum of the four skinfolds. Boys and girls in all groups grew ($p<0.001$) in height and weight: 5.2±2.1 cm and 2.3±1.3 kg in boys and 4.9±2.3 cm and 2.4±1.3 kg in girls. There was no significant change in weight-for-height (data not shown) and MUAC over the treatment period. The MUAC and triceps measurements were converted into upper-arm muscle and fat areas by using Frisancho's formula (23,24). All children showed an increase in upper-arm muscle area, statistically significant for all age, sex and treatment groups compared to baseline (data for treatment groups are shown in Table 3). There was no change in upper-arm fat area between the two measurements. All children also showed a consistent increase in forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC) between the two measurements but no age or sex differences were noted.

Influence of treatment: The increase in height, weight, MUAC, sum of four skinfolds, upper-arm- muscle area and upper-arm-fat areas were not influenced by supplementation with iodine or iron (Table 3). There was also no difference in weight-for-height or height-for-age (data not shown). Similarly, there was no differential improvement in FEV_1 and FVC among the groups indicating lack of influence of supplementation.

Physical stamina and psychomotor development:

The results of the two measures of physical stamina and the five psychomotor development tests are presented in Table 4.

Comparisons not related to treatment: Both measures of physical stamina, hand grip and sitting/standing, increased in all groups over the treatment period but there were no differences between the groups at baseline or after treatment and no age or sex differences. There were no differences at baseline between the groups in any of the psychomotor tests. All children improved their performance on all psychomotor tests (paired t-test, $p<0.001$), except the reaction task test. The tapping test was also administered after 3 mo by which time there was a significant increase in performance ($p<0.001$) but there was no further improvement at the end of the supplementation period. The reaction time increased as tasks became more complex (Table 4, Figure 3) while movement time was the same for all tasks. An age trend was noted for all tests except ball throwing ($p<0.05$ for peg-board and balancing tests for children age 2 yr apart; $p<0.05$ among all age groups for tapping test; and $p<0.01$ among all age groups for reaction time tests). No sex differences in performance of the psychomotor was seen at baseline or after treatment.

Influence of treatment: Supplementation with iodine improved both hand-grip ($p<0.01$) and sitting/standing ($p<0.001$). There was no difference between the groups in the pegboard, balancing and tapping tests. Eye-hand coordination, as measured by ball throwing was increased by both iodine and iron supplementation ($p<0.01$ for single

Table 4 **Effect of iodine and iron supplementation on physical stamina and psychomotor performance***

		Treatment groups			
Test name		Placebo	Iron	Iodine	Iodine & iron
Physical stamina tests		(n=82)	(n=78)	(n=79)	(n=82)
Hand grip (kg)	baseline	6.9±2.9	7.2±2.6	7.0±2.6	6.3±2.2
	final†	9.0±1.7	8.3±1.9	10.3±1.5‡	10.6±1.2‡
Sitting/standing	baseline	46.0±9.5	48.5±9.3	48.6±9.4	47.3±8.8
(n/min)	final†	63.6±6.5	72.1±8.1	91.3±7.0§	94.4±5.2§
Psychomotor tests					
Pegboard (s)	baseline	357.9±65.5	349.1±63.6	352.1±57.6	358.5±60.7
	final†	312.0±50.4	315.2±54.2	305.0±35.8	318.1±49.2
Balancing (s)	baseline	87.0±44.2	87.7±41.3	83.7±45.7	89.0±40.8
	final†	124.1±48.3	123.0±50.7	116.1±47.3	126.2±46.0
Ball throwing (n)	baseline	7.6±2.7	7.5±3.1	8.0±1.8	6.7±3.3
	final†	9.2±3.3	10.3±1.7‡	10.4±2.0‡	11.8±1.4§
		(n=63)	(n=70)	(n=76)	(n=70)
Tapping (n/10s)	baseline	88.4±6.9	87.9±8.8	87.8±8.5	87.6±7.9
	final†	93.7±5.6	93.4±6.6	93.2±5.9	93.7±5.4
Reaction task		(n=52)	(n=62)	(n=63)	(n=64)
A (ms)	baseline	547±150	524±151	558±192	518±146
	final	512±203	467±129	534±172	451±130‡
B (ms)	baseline	932±299	922±319	987±429	949±333
	final	885±304	846±261	919±321	852±296
C (ms)	baseline	1960±569	1954±496	2223±584	1946±521
	final	1745±489	1732±448	1836±464	1754±488

* Mean±SD.
Statistical difference with baseline value on paired t-test:† $p<0.001$.
Statistical difference with placebo group using student's t-test: ‡ $p<0.01$, § $p< 0.001$.

supplementation and $p<0.001$ for double supplementation). Performance in the reaction time task was improved ($p<0.01$) only by double supplementation in the simple reaction task (Task A).

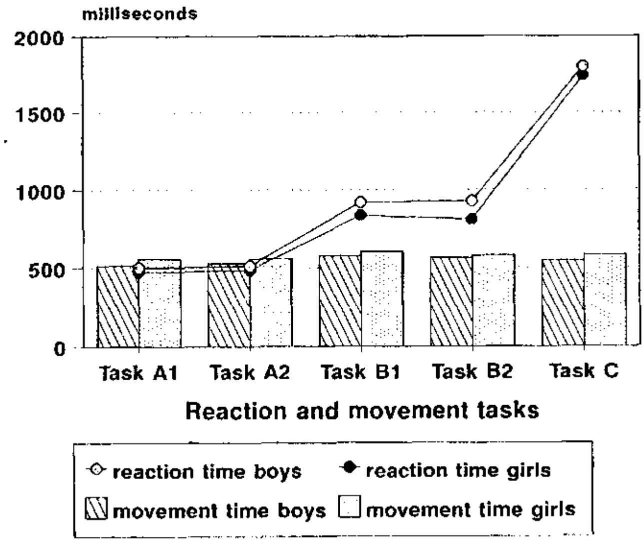

Figure 3
Reaction time and movement time in the three reaction tasks in boys and girls. Tasks A and B were repeated twice.

Discussion

Iodine supplementation increased physical stamina as measured by handgrip and sitting/standing, and eye-hand coordination which was measured by the ball throwing exercise. Iron supplementation increased only eye-hand coordination. Supplementation with iodine and iron together also improved reaction time on the simple reaction task. As far as somatic growth is concerned, neither supplementation with iodine nor iron improved height, weight, sum of the four skinfolds, upper-arm muscle area, upper-arm fat area and lung function.

This is possibly the first time that an effect of iodine supplementation on physical stamina has been demonstrated. Previous studies using a hand dynamometer have not shown such an effect. In one study in Papua New Guinea, children of mothers treated with iodized oil were not different from counterparts from untreated mothers (25) while in a cross-sectional study in Spain (26,27), no difference was seen between children sufficient and those deficient in iodine.

No change in lung function was observed with iodine supplementation. Previous studies of the effect of iodine deficiency on lung function were confined to myxedematous and hypothyroid individuals where thyroid insufficiency resulted in marked muscular weakness leading to respiratory failure (28,29). The lack of effect of iodine supplementation on lung function observed here suggests that thoracic muscles are compromised only when iodine deficiency is severe as in congenital hypothyroids and cretins.

It is well established that severe iodine deficiency before birth can result in growth retardation as seen in cretins, especially of the myxedematous type (1,3). When deficiency is less than that to produce cretinism, the effects are less clear. In an early study in Ecuador, Ramirez et al (30) examined the effect of iodine supplementation on physical growth in children. For two years, they followed groups of children in one village born to mothers who had been injected intramuscularly with iodized oil and compared them with children from another village where mothers had been supplemented with iodine. They concluded that iodine supplementation did not contribute to physical growth of the children. In a recent study in Zaire, Vandenbroek et al (31), compared the height of children aged 2-4 yr with and without goiter and found that those with goiter were taller than their non-goitrous counterparts. The authors attributed the increased growth in the goitrous children to the increased activity of the pituitary which results not only in stimulation of the thyroid gland but also in increased growth hormone secretion. Two previous studies have measured the effect of iodine supplementation on physical growth in children. Israel et al (32) studied children in the same two villages as in the study of Ramirez et al (30) described above. When maturation of the metacarpal of children was examined radiologically before the children were injected with iodized oil and two years later, a small increase in compact bone but not in the degree of ossification or linear growth was observed (31). However the authors concluded that the differences may have been due to other factors. No effect of iodine on physical growth was found in an intervention study in Bolivia (33). Thus our studies are in line with those published earlier which show no effect of iodine supplementation on physical growth.

In this as in other studies (26,27), no effect of iodine supplementation was observed on gross body equilibrium and perseverance as measured by the balancing test but it may be that the test is not sensitive enough to measure minor gains which may be produced.

The central approach to the psychomotor test measuring reaction and movement time is based upon the premise that cognitive activities require a person's deliberate effort and each individual has a limited capacity for such an effort. Reaction time is related to identification of matching geometric shapes and requires cognition of figural units, and a decision. Hence it is dependent upon the complexity of the shapes presented. Once the decision is made, the movement of finger from home to response button, a measure of movement time, falls within a limited time span irrespective of task. Reaction time thus measures the speed at which information is processed and has a greater component of mental development than does movement time which is more related to manual-motor coordination. In the present study, reaction time increased with the number of choices while movement time did not. Reaction time decreased, but not significantly, for all three tasks with age both cross-sectionally and longitudinally while movement time was not related to age. Iodine supplementation had no effect on reaction or movement time. As far as we are aware, the type of equipment used here for measuring reaction and movement time has not been used previously in studies related to iodine deficiency. However, tests have been done in which subjects have been asked to respond to stimuli from light sources. Such studies also have not shown any effect of iodine supplementation (26,27).

Concerning iron, the lack of effect of supplementation with iron on physical growth has been reported by several authors (34,35). In a study in Indonesian children aged 12-18 mo in which mental development was shown to improve with iron treatment, Idjradindata and Pollitt (34) found no change in weight, height and weight-for-height indicating no influence of iron on physical development. Lozoff et al (35) in a longitudinal study of a highly selected group of Costa Rican children (all singletons, birth weight >2.5 kg, without deficiency of iron and B12, without clinical history of infection and growth faltering) also reported no difference in the physical development of children from zero to five years with respect to iron status. However some authors have shown an increase in weight (36). There is a preliminary report from Schultink et al (37) showing increased growth over a 2-mo period when iron supplementation was given to preschool children in Indonesia. As far as lung function is concerned, there have been no studies on the effect of iron nutriture but it may well be that we failed to observe any effect in our study because the iron deficiency was not very severe.

The only effect of iron on psychomotor development we observed was on eye-hand coordination as measured by the ball throwing exercise. Up until now, most attention on the effect of iron nutriture on performance has been directed towards physical strength or mental development while psychomotor development per se has not been the subject of intensive study. In one study in Costa Rica, Lozoff et al (35) compared 5 yr-old children whose iron deficiency had been corrected in the second year of life with children who had not experienced iron-deficiency anemia during infancy. They found that the treated children were still behind with respect to a range of mental and psychomotor tests. The authors interpreted their results to mean that children who have iron-deficiency anemia in infancy are at risk for long-lasting developmental disadvantage as compared with their peers with better iron status. However the differences in mental and psychomotor performance could perhaps be also attributable to other differences between the two groups.

Although both iodine and iron supplementation improved a number of parameters of psychomotor development, no correlations were found between these parameters and iodine or iron status. For iodine, this can be explained by the high between-person variation in urinary iodine concentration which is a poor parameter for evaluating iodine status at the level of the individual. Although blood hemoglobin is a reasonable measure of assessing iron status, the absence of a relationship between hemoglobin level and ball throwing may be due to the fact that the population was not very iron deficient (18% regarded as anemic).

The present findings indicate that supplementation with iodine and iron improve physical stamina and some aspects of eye-hand coordination. As both of these functions are related to body metabolism, it is likely that supplementation produced an improvement in metabolic activity but further work is required to determine how long such effects would last. The results of this study justify current efforts to prevent and treat deficiencies of both iron and iodine in children.

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CHAPTER 3

Supplementation with iodine and iron improves mental development in Malawian children

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(submitted for publication)

Summary

A double-blind placebo-controlled study involving oral dosing with iodized oil and iron was carried out in primary school children aged 6 - 8 yr in Ntcheu District, Malawi in order to investigate the effect of supplementation with iodine and iron on mental development. About 86% of children were at least moderately iodine deficient with urinary iodine concentrations below 0.4 μmol/L and 18% were anemic (blood hemoglobin concentration <110 g/L). Anthropometric measurements were made and seven mental performance tests were administered before and 10 mo after supplementation began. For the measurements of mental development, data were available on 300 subjects. Compared with the placebo group, iodine supplementation increased ($p<0.001$) fluid intelligence (fluency and reasoning), crystallized intelligence (concept development and perception), and perceptual skill (short-term memory and comprehension). Iron supplementation increased fluid intelligence ($p<0.001$) but there was no interaction between iodine and iron supplementation. In terms of IQ, iron supplementation led to an increase of 7 IQ points, iodine supplementation to an increase of 21 IQ points, and a combination of both to an increase of 26 IQ points.

Introduction

Poverty, deprivation and sickness impinge on mental development largely through nutritional status. Probably the most important nutritional factor in such development is the supply of protein and energy which exert their effects both pre and post-partum (1). More recently, it has been shown that deficiencies of micronutrients such as iodine and iron, even when not extreme, can also influence mental development. Studies of iron-deficient infants and children have clearly demonstrated that iron is essential for cognitive development (2). With respect to iodine, all evidence up until now points to a role for this nutrient in the development of the fetus. When iodine deficiency is severe during pregnancy, children can be born cretinous (3).

There has been only one previous double-blind, placebo-controlled study in which the effect of iodine supplementation of children on mental performance has been examined. In that study, Bautista et al (4) found no difference between treated and untreated children in mental performance based on the Stanford-Binet and Bender-Gestalt tests. Other studies on the effect of iodine on mental performance have been comparisons of children in iodine-adequate and iodine-deficient areas (5,6); comparisons of treated children in one area with untreated children in another area (7); cross-sectional studies in populations in which there has been no iodine supplementation (8) or where supplementation has been through the mothers of children examined (9-11); or intervention studies in which the mothers have been supplemented (10,12-16). This raises the question as to whether supplementation of children with iodine can stimulate their mental development.

Since iron deficiency is very widespread, it often accompanies iodine deficiency in populations. Therefore it was decided to study the effect of intervention with both iodine and iron on mental development using a double-blind placebo-controlled design in an area with endemic deficiencies of iodine and iron in Malawi. As there is no common test to judge mental development across different cultures and countries, tests which have been used in various cultures and seemed appropriate to the Malawian situation, were chosen. They do not involve reading and writing skills and thus are assumed to be culture reduced.

Subjects and methods

Study area

The study was carried out in Malawi which is in south-central Africa. The area chosen was in Ntcheu district, a combination of flat land and mountainous terrain, 170 km south of the capital Lilongwe and 185 km north of the commercial city of Blantyre. Approximately 210,000 people of whom 46% were children under 15 yr of age live in the district (17). The study population came from five villages known to be endemic for goitre (18). These villages are inhabited by subsistence farmers of the N'goni ethnic group. None of these villages were supplied with electricity or treated drinking water.

Subjects

Three primary schools, about 9 km from one another, were selected and a complete list of all children admitted to Standards One and Two was obtained. All children (n=424) born between January 1982 and December 1984 were considered for enrolment in the study.

Study design

Several village committee meetings were organized through the local school committees to explain the aims and objectives of the study. Upon verbal approval of the parents, all children selected were medically examined for lung infection, hepatomegalia, splenomegalia, skin infections, pallor and xerophthalmia by a Senior Clinical Officer of Ntcheu District Hospital. No children were excluded on health grounds possibly because seriously sick children do not attend school. Several children with skin infections were treated. The children were stratified by class, age and sex for each school, and then four children from each category were selected at a time for random allocation to each of four groups. The groups were then randomly assigned to four different treatment regimes: placebo; iron; iodine; and iodine plus iron.

The study was double blind with the codes only being broken after the completion of the final test. For the groups not receiving iodine or iron, placebos identical in appearance and composition except for the active ingredient were provided. The iodized oil (Lipiodol UF®; 490 mg I/mL) and placebo (poppyseed oil) were provided by Guerbet Laboratories Ltd (Aulnay-sous-Bois, France) and the iron tablets (ferrous sulphate, 60 mg Fe) and corresponding placebos by Lomapharm Medicines (Rudolf Lohman, Emmerthal, GmHKG Germany). Iodized oil and poppyseed oil were provided as a single dose (1mL) administered orally with an Englass Swift® dispenser (The English Glass Company Limited, Leicester, England) in February 1991. The iron and placebo iron tablets were given in the classrooms by the headmasters of the three schools on weekdays during school term commencing in February 1991 until the completion of the final tests, with a break during the long vacation in August and September. The baseline anthropometric measurements were made and urine samples collected in October-November 1990; the baseline physical and psychomotor tests were performed in November-December 1990; and blood samples collected in January 1991. A second urine sample was taken from the children in April 1991. All measurements and tests, except collection of blood samples, were repeated in October-November 1991. It was not possible to collect blood samples at this time because of opposition from the parents based on unfounded rumours. All tests were conducted between 8:00 and 12:00 during week days in class rooms made available by each school. The study was approved by the Medical Ethics Committees of the National Council for Medical Research of Malawi and the Department of Human Nutrition of Wageningen Agricultural University.

Somatic and biochemical indicators

Height, weight, mid-upper arm circumference (MUAC), triceps and biceps skinfolds were measured in duplicate, as outlined by WHO (19), by one of the authors (RMS) and trained field assistants. Results are expressed as the mean value and, if two measurements differed by a predetermined amount, they were repeated. Height was measured to the nearest mm (Microtoise) weight to the nearest 0.1 kg using an electronic scale (Tefal), skinfolds to the nearest mm by Harpenden callipers (Holtain, Wales) and MUAC to the nearest mm using a flexible steel tape. Urine samples were sent to the Department of Human and Animal

Physiology of Wageningen Agricultural University where they were stored at -20°C prior to analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (20) adapted for use with a microtitre plate reader (Thermomax, Molecular Device Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with Softmax software provided by the manufacturer. All samples were assayed in duplicate and when measurements differed by more than 10% the analysis was repeated. The means of the measurements from each subject at each time point were used for analysis. A blood sample (5 mL) was obtained from the left forearm of all subjects for analysis of hemoglobin (Hemocue, Helsinborg, Sweden), hematocrit (microcentrifuge) and serum ferritin (kit supplied by Boehringer Mannheim GmbH, Germany).

Mental development tests

Seven tests of mental development (Table 1) previously used in studies in very different cultures were administered (21) by high school graduates selected from Ntcheu district and all belonging to the N'goni ethnic group. They were instructed by a psychologist from Chancellor College, Zomba on the objectives of the present study, test materials and test procedures. After initial training, a pretest was organized in a village, away from the study area where each field worker tested at least ten children with the assigned test. Each of three field assistants was assigned to carry out particular tests in separate rooms while a fourth assistant was assigned to collect children from the class rooms and check for completeness of the forms. At the beginning of each battery of tests carried out by a field assistant, a subject was asked to sit comfortably. Distraction by extraneous events or objects were avoided during the tests which were carried out in classrooms devoid of equipment apart from a blackboard, several chairs and a desk. The field assistants explained the tests individually to each subject in the Chechewa language. All tests involving test pictures or drawings had a time limit of 10 s for the child to see the test picture and an additional 10 s to respond to or to identify the answers. If the child did not respond within 10 s, the question was repeated. The test procedure was terminated when a child, on four successive occasions, gave no answer or the wrong answer. Children were not allowed to listen or watch other children being tested. A test-retest study was not carried out because it would not have given a valid picture of the reliability of the instruments due to the learning effects which could be expected at retest. The results of the tests were found to be consistent not only during the pretest but also during the study itself. At the end of each day, all forms were checked for completeness and internal consistency. Seven mental development tests were administered. Except for the fluency test, all tests used books, each with 40 pages of tests.

Fluency in animal and people's names: Each child was asked to recall the names of as many animals as possible in two minutes. After a break of 1 - 2 min, the child was then asked to recall the first names of as many people as possible also in 2 min. The names

Table 1 **Tests used in evaluation of mental development**

Test	Function measured
Fluency, animal names Fluency, people's names	Long-term memory, explicit memory, recollection and recognition.
Exclusion	Reasoning, visual and figural units.
Quantity	Figural relationship, physical properties and concept development.
Verbal meaning	Vocabulary, classification skills, concept development, comprehension and semantic unit.
Visual memory	Short-term visual memory and perceptual speed.
Closure	Figural unit, perceptual speed and reconstruction.

Adapted from reference 21.

given by the child were recorded by the field assistant and each name of an animal or person was scored as one point.

Exclusion: Each test page had four abstract pictures, three of which had a common characteristic. The child was asked which one of the four pictures did not belong to the group and each correctly identified picture was scored as one point.

Quantity: Each test page had four to six drawings with relative meanings such as many and few, big and small, long and short, far and near, and more and less. The child was asked which of the pictures was big or small, etc. depending upon the context of the test picture. Each correct identification was scored as one point.

Verbal Meaning: Each test page had two to four drawings. The child was asked to distinguish between amount and fullness, amount and size, amount and length, etcetera and such differentiation is the basis for the test. The tasks varied from "choose the longest skipping rope" to "in which glass is the most lemonade" to "in which row are the most red balls". Each correct answer was scored as one point.

Visual Memory: Each test page had one abstract picture while a solution page immediately after had four to eight abstract pictures including the test picture. Each child was shown the test picture for 10 s and the book then closed for about 2 s. Then the book was opened on the solution page and the child was given up to 10 s to indicate which test picture had been

Table 2 **Characteristics of children enroled in the study at baseline**

	Treatment groups			
	Placebo	Iron	Iodine	Iodine & iron
Family characteristics	(n=72)	(n=81)	(n=77)	(n=78)
Children (n)	4.2±1.5	4.2±1.8	3.8±1.5	4.3±1.7
Household size (n)	8.0±2.7	7.6±2.7	7.7±2.7	7.8±2.6
Cattle and goats (n)	6.5±8.8	6.5±6.0	5.4±5.4	5.0±5.3
Family land (ha)	0.76±0.45	0.72±0.50	1.04±0.60	0.76±0.50
Characteristics of children	(n=67)	(n=74)	(n=74)	(n=79)
Age (y)	7.1±0.7	7.1±0.8	7.1±0.8	7.1±0.8
Height (cm)*	116.7±6.8	115.4±6.8	115.4±6.5	116.5±7.3
Weight (kg)*	20.5±2.4	19.5±2.5	20.1±2.6	20.5±3.0
MUAC (cm)	17.0±1.1	16.9±1.3	17.1±1.4	17.0±1.2
Sum of four skinfolds (mm)	19.0±4.0	18.5±4.1	19.9±3.4	19.0±3.7
	(n=72)	(n=81)	(n=77)	(n=78)
Haemoglobin (g/L)†	121 (117, 128)	120 (110, 128)	121 (111, 127)	119 (114, 128)
Haematocrit (%)†	0.38 (0.36, 0.41)	0.38 (0.35, 0.40)	0.37 (0.25, 0.40)	0.38 (0.35, 0.40)
Serum ferritin (μg/L)†	38.5 (25.2, 63.2)	47.0 (27.0, 64.2)	39.5 (21.2, 75.5)	40.0 (24.2, 61.0)
Urinary iodine (μmol/L)†	0.15 (0.09, 0.26)	0.16 (0.07, 0.30)	0.15 (0.09, 0.25)	0.15 (0.08, 0.26)

Mean±SD. There were no differences between the four treatment groups in any of the parameters measured (ANOVA).

* The mean height and weight of the subjects were significantly lower than NCHS standards ($p<0.001$).

† Median (25th, 75th percentiles).

seen. Each correct identification was scored as one point.

Closure: Each test page had one incomplete drawing of everyday objects such as personal effects, household appliances, furniture, animals, and objects in the surroundings such as trees and roads. The child was shown each page in turn and asked to identify the partlycompleted object, a task requiring mental reconstruction of what was missing. Each object correctly identified was scored as one point.

Standardization of scores

The raw scores of the individual tests were standardized to a mean of 15 and SD of 5 based on all the results after the intervention. In addition, the raw scores of all tests were combined and standardized to a mean of 100 and SD of 15. The tests were also aggregated and standardized in the same way to estimate scores (23) for fluid intelligence (fluency and exclusion), crystallized intelligence (quantity and verbal meaning) and perceptual skills (visual memory and closure).

Statistical analysis

The statistical analysis was carried out on the group means of the four treatment groups using Student's t-test. Analysis of variance was used to examine interactions between effects of iodine and iron.

RESULTS

As shown in Table 2, there was no difference among the treatment groups in average number of children, number of household members, number of domestic animals owned (cattle and goats) and land for each family of the children in the study. The age, height, weight, sum of four skinfolds, MUAC sum of 4 skinfolds were similar among the four groups at baseline. Overall 27% of children were stunted and 2% wasted. There was no difference in urinary iodine concentration, blood hemoglobin, hematocrit and serum ferritin. The mean urinary iodine concentration of 0.22μmol/L in the total population indicated that the population was moderately iodine deficient (22): 52% had urinary iodine concentration <0.16 μmol/L (severe iodine deficiency); 34% with values 0.17 -0.40 μmol/L (moderate iodine deficiency); and 11% with values 0.41 - 0.79 μmol/L (mild iodine deficiency). Based on hemoglobin <110 g/L and hematocrit <0.35, the number of children classified as anemic was 18% and 16% respectively. Iron stores, as determined by serum ferritin levels <20 μg/L were depleted in 16% of the children.

After 3 mo, urinary iodine concentration increased in the iodine and iodine plus iron groups from a median of 0.15 (0.09, 0.25; 25th and 75th percentiles) μmol/L and 0.15 (0.08, 0.26) μmol/L to 0.42 (0.01, 1.19) μmol/L and 0.32 (0.11, 0.84) μmol/L respectively. After 11 mo, the values had fallen to 0.18 (0.08, 0.50) and 0.16 (0.06, 0.34) μmol/L respectively. There was no change in the other two groups which did not receive iodized oil. The change in haematological indices could not be verified due to objections in drawing subsequent blood samples.

About 25% of children were not followed up because they left school. The mean height, weight their family characteristics and various mental development scores of children who dropped out of the study and those who continued were not statistically different. According to the district primary school registers, 20% to 40% annual dropouts are normal in primary schools in Malawi.

The results presented here are only for those children who completed both measurements and tests. The scores for all the mental development tests at baseline were not different among the groups (data not shown). After the treatment period, scores for some of the tests increased markedly in all groups including the placebo group. Although in the placebo group, the scores for the fluency test for animal names were almost identical for the 6-yr and 7-yr old children, the score of the 6-yr old children increased by 60% when measured one year later. The increase in the score for the fluency test for people's names was 30% while that for the other tests was somewhat less ranging from 2 to 14%. Therefore, because of the marked learning effect, especially for fluency, it was decided to base the data analysis on the final tests (Table 3) and not on the increase over the period of supplementation.

Effects not related to treatment:

No difference was observed between boys and girls except for the closure test where boys performed better than girls ($p<0.05$). Older children had better performance for quantity, verbal meaning and exclusion but not for fluency, visual memory and closure, indicating an improvement in concept development, vocabulary and reasoning but not in memory and perception. For quantity, both 7-yr old children ($p<0.05$) and 8-yr old children ($p<0.01$) had significantly higher scores than 6-yr old children; for verbal meaning 8-yr old children scored significantly better ($p<0.01$) than 6 and 7-yr olds; while for exclusion, 8-yr old children had higher scores than 6-yr olds ($p<0.01$).

Effects related to treatment:

There were marked effects of both iodine and iron but no interactions were observed (ANOVA). *Fluency* for both animal and people's names improved in children receiving iron ($p<0.05$) compared with the placebo group, but an even greater effect was seen in the children in the groups receiving iodine ($p<0.001$ compared with both the placebo and iron groups). Iron supplementation and iodine supplementation both increased the results for *exclusion* compared with the placebo group with the effect being more marked in the group receiving both iodine and iron ($p<0.001$) than when only one nutrient was supplied ($p<0.05$). For *quantity*, both iodine (<0.01) and iron ($p<0.05$) improved the scores compared with placebo. Neither iron nor iodine alone increased *verbal meaning* compared with the placebo group. However, the group receiving both iodine and iron had a higher performance ($p<0.01$) than all other groups. Children receiving iodine, with or without iron, had increased *visual memory* scores compared with the placebo and iron groups ($p<0.001$).

For *closure*, the groups receiving iodine had improved performance compared with placebo ($p<0.05$ for iodine alone; $p<0.01$ for group receiving both iodine and iron) but iron had no effect.

Table 3 **Mean scores of selected mental development tests by treatment groups***

	Treatment groups			
	Placebo (n=72)	Iron (n=76)	Iodine (n=72)	Iodine & Iron (n=80)
Fluency, animal names	10.2±3.4	11.7±2.8†	18.5±2.8§	19.2±2.7§
Fluency, people's names	10.5±4.3	12.6±4.2†	17.7±3.1§	18.6±4.2§
Exclusion	12.1±6.3	15.9±3.9†	15.2±4.7†	16.4±3.7§
Quantity	13.4±5.7	15.1±4.7†	15.6±5.1‡	15.8±4.1‡
Verbal meaning	14.3±5.3	14.5±4.8	14.3±5.1	16.3±4.7‡
Visual memory	12.3±6.0	13.2±4.1	16.8±3.9§	17.5±3.5§
Closure	14.4±4.8	13.1±4.9	16.3±4.1†	16.5±4.5‡
Aggregated scores ‖				
Fluid intelligence	10.7±2.4	13.5±1.9§	17.1±1.8§	18.2±1.5§
Crystallized intelligence	13.8±4.6	14.7±3.5	15.2±3.6‡	16.1±3.0§
Perceptual skill	13.3±4.3	13.2±3.4	16.5±3.3§	16.5±2.9§

* Mean±SD.
Student's t-test levels of significance compared to placebo group:
†p< 0.05, ‡p< 0.01, § p< 0.001.
‖ Aggregated scores adapted from reference 23: fluid intelligence, fluency and exclusion; crystallized intelligence, quantity and verbal meaning; and perceptual skill, visual memory and closure.

Fluid intelligence (23) is often considered to be one of the major constituents of intelligence; it is often associated with fluency, exclusion, and deductive reasoning as measured by series extrapolations and syllogisms. In the present battery both fluency tests and exclusion measure fluid intelligence. Both iodine and iron increased fluid intelligence ($p<0.001$) with the effect being more marked with iodine ($p<0.001$ when the iodine and iron groups are compared). *Crystallized intelligence* (23) involves the expression of intellectual abilities in a specific context. While fluid intelligence refers to learning capacities, crystallized intelligence refers to what people have learned in the past. Tests of vocabulary and arithmetic are examples of frequently applied measures of crystallized intelligence. In the present battery, crystallized intelligence is represented by quantity and verbal meaning.

The iodine and the iodine plus iron supplemented groups showed significantly higher scores ($p<0.001$) on crystallized intelligence than the control group. Iron supplementation alone did not result in a significant increase in score. *Perceptual skills* (23) were tapped by two tests of the battery, namely visual memory and closure. As for crystallized intelligence,

Table 4 **Correlation coefficient between various mental development tests** within the placebo group (n=72)

	Mental development tests						
	1	2	3	4	5	6	7
1. Fluency, animal names	1.00						
2. Fluency, people's names	0.41‡	1.00					
3. Exclusion	0.38†	0.20	1.00				
4. Quantity	0.15	0.11	0.36‡	1.00			
5. Verbal meaning	0.11	0.12	0.03	0.45‡	1.00		
6. Visual memory	0.05	0.09	0.26*	0.28*	0.23	1.00	
7. Closure	0.11	0.13	0.15	0.34†	0.26*	0.22	1.00

Significance of correlation coefficient: *$p<0.05$, †$p<0.01$, ‡$p<.001$

supplementation with iodine improved perceptual skill performance ($p<0.01$) while iron did not.

Inter-relationship between scores and relation with biochemical parameters

The highest correlations between the various tests were found within each of the three categories: within fluid intelligence, fluency for animal names was correlated with fluency for peoples names ($p<0.001$) and exclusion ($p<0.1$); within crystallized intelligence, quantity was correlated with verbal meaning ($p<0.001$); while within perceptual skills, the correlation between visual memory and closure just failed to reach significance (Table 4). The magnitude of the effect on various aspects of intelligence can be obtained by expressing the differences of the experimental groups with the control (placebo) group in terms of the pooled within-group standard deviations of the control and experimental group. Based on a standard deviation of 15 for intelligence quotient (IQ), values shown in Table 5 are obtained. The overall influence ($p<0.001$) of iron is 7 IQ points, of iodine 26 IQ points and of the combination of iron and iodine, 26 IQ points. Moreover, fluid intelligence is more

Table 5 **Effect of iron and iodine treatment in terms of intelligence quotient (IQ)***

	Treatment groups			
	Iron (n=76)	Iodine (n=72)	Iodine & Iron (n=80)	Mean
Fluid intelligence	19.46	45.25	56.87	40.53
Crystallized intelligence	3.31	5.08	8.98	5.79
Perceptual skill	-0.39	12.52	13.22	8.45
Mean	7.46	20.95	26.35	18.26

affected by supplementation than crystallized intelligence and perceptual skills. Iodine has a marked effect on fluid intelligence.

Although the population was markedly deficient in iodine, there was no correlation of aggregated or individual mental development scores with the concentration of iodine in urine at baseline. Similarly there was no correlation between the iron parameters at baseline and the mental development tests either individually or aggregated.

Discussion

This study is the first to demonstrate a clear stimulatory effect of supplementing children with iodine on their mental development. In all aspects of mental development measured (fluid intelligence, crystallized intelligence and perceptual skill), iodine supplementation was effective. With respect to iron supplementation, fluid intelligence was increased.

In previous studies in which mental and psychomotor skills were measured in children after iodine supplementation, no significant stimulation was found (4,5,7,16). In one study (7) there was a significant effect in girls, but not boys, if a one-tailed t-test was applied. The lack of definite positive results in previous studies could perhaps be attributed to the wide age range and limited number of subjects studied and the limited number of tests used. However, the mechanisms involved in the effects observed in the present study cannot be easily explained. Supplementation with iodine has most likely increased metabolic activity of the children resulting in higher activity of the central nervous system. In addition, it may have reversed anatomical damage. It is not possible to test either of these hypotheses using the present study population because they live in an area now covered by the national iodine deficiency control program.

Since this study is double-blind and placebo-controlled in design, it is unlikely that the effects observed are due to extraneous factors. Among the four groups of children, there were no differences in any of the baseline parameters measured (Table 2). In addition, children in the groups which received the iodized oil had increased concentrations of iodine in the urine three months after dosing while those who received the placebo demonstrated no such increase. Unfortunately we have no data on iron status of children during intervention but we have no reason to believe that the supplementation with iron and the placebo did not go to the children for whom they were destined. Data after the period of supplementation were not available from about 25% of children who entered the study but this reflects the normal annual rate of dropout from primary school in the area and was taken into consideration during the design of the study. There is no evidence that those children who withdrew from the study were different from those who were followed up or that the characteristics of the treatment groups were differentially affected. The number of subjects in each group was sufficient to obtain unequivocal results. Thus, we now have data both on the within-group and among-group variation of the various parameters of mental development. This will be useful in calculating the number of subjects required per group in future studies.

Most studies up until now have indicated a role of iodine in prenatal development. When iodine deficiency is severe during the prenatal period, it leads to impairment of central nervous system development which, in its most severe form, results in cretinism (3). Intervention studies in Ecuador (13-15) and Zaire (16) have shown that moderate iodine deficiency during pregnancy impairs mental development of children. Therefore up until now, it has generally been accepted that mild iodine deficiency exerts its effects prenatally and that the effects seen are part of the continuum which, in its most severe form results in cretinism (24). Results from cross-sectional (8) and ecological studies (5,6) are consistent with such a hypothesis even though they do not rule out a post-partum effect of iodine on mental development.

In this study, iodine supplementation was associated with an increase in three aspects of mental development: fluid intelligence, crystallized intelligence and perceptual skills. The earlier studies with pre-natal iodized oil supplementation have shown an increase in some but not all aspects of mental development. In Ecuador, significant improvement was shown in general school performance (13) and intelligence as measured by the Stanford-Binet test (14,15) but not in the Raven test which also measures general intelligence and in the Wechsler and Bender-Gestalt comprehensive mental performance tests (13). In Zaire, a significant improvement in development quotient as measured by the Brunet-Lizine test was seen in children <8 mo in age but not those aged between 8 and 23 mo (16). In ecological studies in Indonesia (5), Spain (5) and China (6) and an intervention study in Ecuador (7) where children in one village were treated while those in another were not, significant improvement in mental performance as measured in several tests was seen.

It is interesting to note in this study that fluid intelligence is stimulated to a greater extent than is crystallized intelligence, This is quite the opposite to that seen as a result of training where crystallized intelligence is stimulated more than fluid intelligence (25). This is understandable as training is more likely to increase the number of facts known than ability to reason. Further studies will be required to examine this finding.

In this study, no relationship was found between the concentration of iodine in urine at baseline with the mental development scores either individually or when grouped into fluid intelligence, crystallized intelligence and perceptual skills. This is to be expected because a single measurement of urinary iodine concentration is a useful parameter for characterizing a population but not individuals because the intra-person variation is too great.

The dose of iodised oil used (1 mL Lipiodol® UF containing 490 mg iodine as ethyl esters of iodized fatty acids of poppyseed oil) was not adequate to maintain normal urinary iodine levels for one year. At the end of the intervention period, urinary iodine levels had returned to the initial levels. In other studies, we have shown that a preparation based on the glyceryl esters of iodized fatty acids containing the same amount of iodine (Oriodol®, Guerbet Laboratories) was more effective (26). It may well be that serum levels of thyroxine (T4) and triiodothyronine (T3) were still elevated one year after dosing with iodized oil even though urinary iodine levels had returned to baseline values.

Deficiency of iron has been linked with development delay in infants (27) and sub-optimal performance in school children in various tests of IQ and school performance (28,29). Lozoff et al (27) examined 5-yr old children whose anemia in the second year had been corrected. Their mental performance had not caught up to that of peers who had not suffered from anemia. Although this would suggest that the effects of anemia were not reversible, it may well be that the children differed in respects other than having anemia as infants. A number of double-blind placebo-controlled studies have been carried out in Thailand (29) and Indonesia (28,30,31). Two of the studies showed a significant increase (28,31) in mental performance while two did not (29,30). In the studies in which positive effects were seen, the age of the children was 12 - 18 mo (31) and about 5 - 6 yr (28) while in the studies in which there was no effect (29,30), the children were somewhat older (about 10 yr in both studies). A positive effect was only seen in children who were initially anemic (28,31). In our study, we found only a limited effect of iron supplementation on mental development probably because the children were older (mean age 7.1 yr) and the prevalence of anemia was not high (18% of children with hemoglobin <110 g/L). This emphasises the need to treat iron deficiency in children as early as possible in order to reverse the deleterious effects of anemia on mental development.

The total standardized score represents a sum of the scores on fluid intelligence, crystallized intelligence and the perceptual skills which constitute various components of general intelligence. The correlations between the tests included in the three categories of aggregated tests were significant ($p<0.001$; $r = 0.28 - 0.43$). Hence, it would appear to be valid to aggregate the tests into the three components of intelligence. The standardized total mental development score of the iodine treated groups was found to be 21 points (1.4 SD) higher than the placebo group. This score is not completely analogous to an IQ score but nevertheless, the present finding clearly implies that iodine supplementation has a strong positive impact on fluid intelligence, crystallised intelligence and perceptual skills of school children and justifies iodine supplementation of this segment of the population, if iodine deficient.

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CHAPTER 4

Role of iodine in mental and psychomotor development: an overview

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Over the past few decades, our understanding of the relationship of protein-energy malnutrition (1), iron-deficiency anaemia (2) and iodine deficiency (3) with mental development and the overall well-being of infants and children has increased. Over the past few decades, our understanding of the relationship of protein-energy malnutrition (1), iron-deficiency anaemia (2) and iodine deficiency (3) with mental development and the overall well-being of infants and children has increased. The concept that various degrees of iodine deficiency can impinge on physical and mental development was crystallized in the sentinel paper of Hetzel in 1983 (3) even though the link between iodine deficiency and problems related to the thyroid has been recognized for many centuries (4). The disappearance of goiter and cretinism in several countries in Europe and Latin America with the introduction of iodized salt raised several scientific questions on the magnitude and role of iodine deficiency in mental and psychomotor development.

Experiments with sheep, marmosets and rats have shown that iodine deficiency is related to fetal development as indicated by reduced brain weight, reduced birth weight and delayed fetal maturation (5). The knowledge acquired from animal models cannot be extrapolated readily to human beings because of the differences between man and animals in psycho-sensory and social responses to stimuli. However, evidence from animal studies (5,6) and from a limited number of studies on brain development in human fetuses (7) indicate that iodine deficiency can impair brain development.

Given that malnutrition has a negative effect on mental and psychomotor development, the question arises to what extent such effects are reversible. Deficiency of a specific nutrient at a critical time may produce specific lesions in the brain and perhaps other regions of the central nervous system resulting in permanent mental retardation. This model does not take into account stimulation from other environmental factors and adaptive mechanisms referred to as plasticity of mental development. It also does not take into account individual differences both in response to external factors and to adaptation. Thus the concepts of *critical point* and *catch-up behaviour* have been introduced. As far as critical point is concerned, both the magnitude of the insult in relation to the individual's ability to withstand the insult and its timing with respect to iodine deficiency are involved.

There are also methodological difficulties in assessing the effect of nutrient deficiencies in general and iodine deficiency in particular on mental development. On the one hand, there are problems related to the tests of mental development with respect to specificity, validity, and appropriateness of test materials and procedures and on the other hand, the measurement of iodine status both at the population and individual level is thwart with difficulties.

Conceptual analysis

Malnutrition with respect to protein and energy and to micronutrients impinges on the individual and its effects are observed throughout the life cycle perhaps extending as far back as conception. Deficiencies of protein and energy and of iron and iodine during the prenatal period have been linked with a high incidence of spontaneous abortion and low-birth-weight children, and compromised immune competence and mental performance. The effects of such deficiencies during the postnatal period have been linked with stunting, wasting, inappropriate immune response resulting in increased incidence and severity of infections, and impaired physical and mental development. The mechanism by which iodine deficiency impairs mental development is poorly understood. Based upon available empirical data, the relationship between various environmental factors and mental development can be conceptualized as outlined in Figure 1 in which there are factors related to iodine and others which are not.

During the prenatal period, the fetus is totally dependent upon the mother including for the supply of nutrients. After birth, nutrients continue to be supplied by the mother but this dependence decreases with time. As the child grows, various environmental and social factors, such as food availability, exposure to infection, parental income and education, and services including education, health and communications, influence a child's development. Social stimulation, involving interaction with family in particular and society in general, contributes to shaping a child's mental development. It is within this context that mental development, which can be extended to include psychomotor development, is influenced by iodine nutriture.

Iodine and the thyroid gland.

Iodine exerts its function in the body only when it is incorporated into thyroid hormones and the processes in these hormones and the control mechanisms involved are reasonably well understood (8) as is the physiological role of the thyroid gland in relation to various body functions (9,10). There is now adequate evidence to link iodine deficiency with

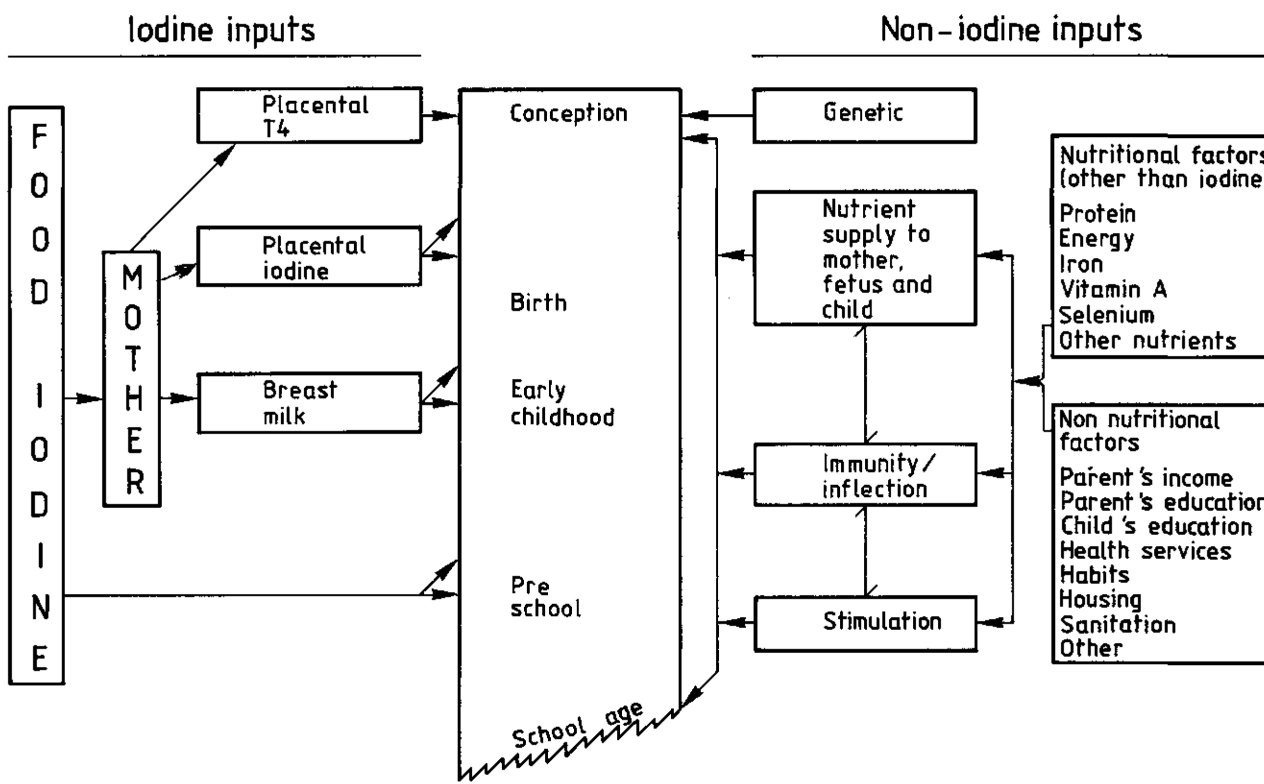

Figure 1
Pathways of iodine and non-iodine inputs during fetal and child development

impairment of the maternal and fetal endocrine system (11,12) and consequent mental deficiency in the new-born, which in its most severe form leads to cretinism (13). The effects of prenatal iodine deficiency on a child continue throughout life and superimposed on these are the effects of postnatal iodine deficiency (Figure 1). Iodine is incorporated into the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Initially the fetus is dependent on the mother for preformed T4 but after about 3 months, the fetus begins to become independent of the mother for T4 as it is able to synthesize its own from iodine supplied via the placenta.

It is generally agreed that mental deficiency is the most serious outcome of thyroid insufficiency arising from iodine deficiency (3,10). Cretins, be they due to iodine deficiency or not (sporadic), are obviously mentally deficient (3). Studies have shown that iodine deficiency can also cause less obvious intellectual deficits in non-cretins (3,14-18). Whether such individuals are called sub-cretins (17) or mentally sub-normal is a matter of definition. Three fundamental questions still remain to be answered: what is the critical age at which the exposure to iodine deficiency causes mental deficiency, what minimum length of exposure to iodine deficiency is necessary to cause mental deficiency, and to what extent can mental deficiency caused by iodine deficiency be reversed?

Iodine deficiency and cretinism

A condition which later became known as cretinism was first described by Felix Platter towards the end of 16th century in Switzerland. The word cretinism was first introduced in Diderot's Encyclopedia in 1754 which described the condition of an imbecile who was deaf and dumb and had a large goiter hanging in the neck (4). The term *cretinism* redescribed by McCarrison in 1908 (19) includes deaf-mutism, mental retardation, and characteristic spastic or rigid neuro-motor disorders, abnormal somatic development with disproportionate body and facial characteristics, growth retardation and hypothyroidism.

Using the broad terminology of McCarrison, two types of cretinism can be defined (20,21). The first type is *neurological cretinism,* characterized by deaf-mutism, mental retardation and neurological disorders with extensive damage to the motor and auditory systems. The second type is *myxedematous cretinism* characterized by stunted growth, continuing myxedema, coarse facial features, severe musculo-skeletal disorders accompanied by hypotrophic muscles, congenital hypothyroidism, and psychomotor retardation but usually not accompanied by deaf-mutism or severe mental retardation. The myxedematous type of cretinism is found mostly in areas where endemic iodine deficiency is coupled with consumption of goitrogenic substances such as cassava (16), which inhibit iodine uptake. The two types of cretinism may exist in the same locality and even in the same individual

(20). Both types of cretinism can be prevented by administering iodized oil during pregnancy (22). It is believed that severe iodine deficiency in pregnant mothers during the first trimester of gestation results in neurological cretinism while severe iodine deficiency in the second half of pregnancy results in myxedematous cretinism. In neurological cretinism, there is no maternal/fetal hypothyroidism and the condition is not reversible by administration of T4, or as would be expected by iodine itself. Neurological cretinism is more frequent among mothers with large goiters. This suggests that the pathogenesis of neurological cretinism is different from that of myxedematous cretinism in which mental retardation appears to be the consequence of hypothyroidism during the late fetal and/or neonatal period (22). Such hypothyroidism can be reversed by T4 or by iodine provided that it is sufficient to produce normal levels of T4 (10). Elevated levels of T3, which occur when T4 levels are depressed, cannot reverse neurological lesions (10). Even though much of the effect of myxedematous cretinism can be reversed in the second half of pregnancy, correction of iodine deficiency at this time in sheep results in lambs with brains of normal size but with reduced number and length of neurones (6). The signs and symptoms of neurological involvement in cretinism is detectable even when it is mild (14).

Iodine status and mental performance

With the spontaneous disappearance of cretinism and decline in deaf mutism in Italy and Switzerland following the introduction of iodized salt, controlled trials were commenced in 1966 in Papua New Guinea (Studies 1-5 in Table 1) and in Ecuador (Studies 6-9) to see whether endemic cretinism could be prevented by supplementation with iodine. These were the first of quite a number of studies on the role of iodine in mental and psychomotor development which can be classified into four categories: cross-sectional, intervention, case-control and ecological studies. The results of the research work carried out by Pharoah, Connolly and colleagues in a population in iodine-deficient areas in Papua New Guinea were analyzed both in the form of cross-sectional studies (Studies 1-3) and intervention studies (Studies 4 & 5). Some of the intervention studies were carried out in the same area (Studies 4,5,7,8,14,15 & 17) while some were carried out in different populations (Studies 6-9 & 12). In many of the intervention studies, mothers were dosed with iodized oil (Studies 4,5,7-9, & 14) while in some studies, the children were given iodized oil (Studies 6-8,12,15 & 17). The case-control study (Study 10) compared goitrous and non-goitrous children while the ecological studies have compared populations in iodine-deficient and iodine-sufficient areas (Studies 11,13 & 16). The above studies were carried out in China, Indonesia, Papua New Guinea, Bolivia, Chile, Ecuador, Malawi, Zaire and Spain using a variety of tests to measure mental and psychomotor development.

Table 1: **Inventory of studies on the effect of iodine on psychomotor and mental development***

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
1.	Pharoah et al (28); Papua New Guinea	10-12 (20)	Mothers injected (4mL) in 1966 with iodized oil or placebo and children tested in 1980-81; analyzed as cross-sectional study	Pegboard, bead threading, peg frame, Pacific design	Psychomotor performance correlated with maternal T4 during pregnancy
2.	Connolly & Pharoah (26); Papua New Guinea	14-16 (22)	Children of treated mothers referred to above tested in 1985; analyzed as cross-sectional study	Pegboard, bead threading	Psychomotor performance correlated with maternal total T4 during pregnancy
3.	Pharoah et al (24); Papua New Guinea	6-12 (208)	Population as above, children tested in 1978; analyzed as cross-sectional study	Hand grip, dotting, bolt nutting, pegboard	Psychomotor performance correlated with maternal total T4 but not total T3 during pregnancy
4.	Pharoah et al (27); Papua New Guinea	11 & 15 (28-30)	Population as above, children tested in 1978 and 1982; analyzed as intervention study	Hand grip, tapping, dotting, bead threading, pegboard threading, Pacific design construction	No difference between children of treated (n=11-13) and untreated mothers (n=15-18)

* non cretinous population

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
5.	Connolly et al (25); Papua New Guinea	Children, age ? (194)	Population as above, children tested in 1978; analyzed as intervention study (treated, n=115; control, n=79)	Hand grip, tapping, dotting, bolt nutting, bead threading, pegboard	No difference in hand grip, tapping, dotting, and bolt nutting between two groups; children born to treated mothers performed better in bead threading and pegboard
6.	Dodge et al (31); Ecuador	6-10 (96)	Intervention study: children in one village (n=51) injected with iodized oil (2mL) and compared after 2 yr with those in control village (n=45)	Goddard, Goodenough Draw-A-Man	Mental development of treated children tended to be better than controls; statistically significant only for girls using one-tailed test
7.	Fierro-Binetz et al (32); Ecuador	Children age >40 mo (150)	Intervention study: mothers injected with iodized oil (4mL) during early (n=41) or late pregnancy (n=26); matched children in control village (n=83) injected with iodized oil (0.5mL)	Stanford-Binet	Children of mothers treated early in pregnancy had better mental performance than children of mothers injected late in pregnancy and children from control village

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
8.	Trowbridge (30); Ecuador	2-8 (125)	Intervention study: mothers injected with iodized oil (4mL): children born 0-9 mo before (n=35); 0-9 mo afterwards (n=44); 9-18 mo afterwards (n=46)	Stanford-Binet	Treatment of mothers prior to conception or during gestation improved subsequent mental performance of children compared to children who were not treated until after birth
9.	Fierro-Binetz et al (33); Ecuador	8-15 (421)	Intervention study: mothers in one village injected with iodized oil (4mL); children (n=128) compared with matched children (n=293) in control village	School performance, Terman-Merrill, Goddard, Goodenough Draw-A-Man, Wechsler, Bender-Gestalt, Raven (not all subjects undertook all tests)	Children from treated mothers had better school performance, psychomotor development indices and Draw-A-Man test; no significant difference in Bender-Gestalt, Terman-Merrill, Wechsler and Raven tests

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
10.	Muzzo et al (34); Chile	School-aged children (90)	Case control study: comparison between goitrous (n=42) and non-goitrous (n=48) children matched for nutritional status	Wechsler, Bender-Gestalt Koppitz, pegboard	Performance of non-goitrous children higher than goitrous children, no difference in visiomotor coordination and hand skills
11.	Bleichrodt et at (35); Indonesia and Spain	Indonesia, 6-20 (245); Spain, 0-12 (255)	Ecological studies: comparison between children in iodine deficient and non-deficient areas	Maze, fluency, visual memory, figural unit, handgrip, comparison, exclusion, peg-, board, balancing, tapping, Bender-Gestalt	Subjects from iodine deficient areas: <2.5 yr, no difference in mental, Raven and psychomotor scores; 2.5-5 yr and 6-12 yr, lower mental and psychomotor scores; 13-20 yr, lower mental scores; no difference in eye-hand coordination

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
12.	Bleichrodt et at (36); Spain	0-5 (205)	Intervention study: children given one dose (2mL) iodized oil in one village (n=103) and compared with untreated children (n=102)in matched village	As above	No effect of treatment
13.	Boyages et al (37); China	7-35 (379)	Ecological study: comparing individuals in 3 areas differing in access to iodized salt: rural areas with and without iodized salt, urban areas with iodized salt	Hiskey-Nebraska, Griffiths	Mental performance in urban children> rural children with iodized salt > rural without iodized salt

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
14.	Thilly et al (38); Zaire	4-23 mo (75)	Double blind intervention study: mothers injected (4mL) with iodized oil (n=36) or placebo (n=39) at 28 w gestation	Brunet-Lizine	Mental performance higher in children aged 4-8 mo but no difference in children aged 10-15 mo and 16-23 mo
15.	Bautista et al(39); Bolivia	5-12 (200)	Double blind intervention study; children with thyroid enlargement dosed orally (1mL) with iodized oil (n=100)	Stanford-Binet, Bender-Gestalt	Goiter rate lower in treated group no difference in physical and mental performance and school performance

(continued)

Study No.	Reference; Study site	Age yr, (n)	Study design	Tests used	Results
16.	Ma (17); China	Primary school children (4392)	Ecological studies: comparison between children in 13 iodine deficient areas with those in control areas	Stanford-Binet Wechsler	Children from iodine-deficient areas had lower IQs
17.	Shrestha et al (47,48); Malawi	6-8 (241-321)	Double-blind placebo-controlled study: children dosed orally with iodized oil (1mL) or placebo	Fluency, exclusion, verbal meaning, visual memory, closure, handgrip, sitting-standing, pegboard, balancing, ball throwing, tapping reaction time	Mental development, hand grip, sitting-standing, and eye-hand coordination improved in treated children, no difference in other psychomotor tests

The studies carried out by Pharoah and colleagues (Studies 1-5) were based upon a single dose of 4ml of Neohydriol® (equivalent to 2.15 g of iodine) or placebo given intramuscularly to a population of over 16,000 people living in 27 villages. Iodized oil or saline was given to alternate families in the study area. Longitudinal observation of children born to mothers in these villages has provided extensive data on various aspects of iodine deficiency disorders and the effects of iodine supplementation (23). A total of 946 children were born, 412 to treated mothers and 534 to the saline group mothers. Seven cretins were born to the iodine-treated mothers of whom 6 were conceived prior to treatment (the time of treatment in relation to conception was not known in the seventh) while 26 cretins were born to the untreated mothers of whom 5 were conceived prior to injection. This work clearly demonstrates that iodine deficiency is the prime cause of endemic cretinism (23).

From the women participating in the above study, blood samples were collected from 106 women, of whom 66 were pregnant at the time. Between 1966 and 1971, 149 children were born to this group of women. The results (29) indicate a higher rate of pregnancy wastage in mothers with very low total T4 (<25ng/ml), low free T4 (<10pg/ml), low total T3 (<850pg/ml), and elevated TSH (>10ug/ml).

In three cross-sectional studies (Studies 1-3), psychomotor performance of children, measured using a selection of tests, was correlated with maternal T4 during pregnancy. The authors concluded that maternal T4 and not T3 may be essential for normal neurological maturation of the fetus before the thyroid of the fetus becomes functional. The correlation between maternal T4 and maturation of the fetus raises the question: is there a close relationship between the neurologic integrity of fetus and the maternal thyroxine level during pregnancy and the motor performance of the child later in life? A more plausible model might be that there is a threshold effect, given that sufficient hormone is available at an appropriate time during fetal life, brain development continues normally. Any insufficiency in hormone availability is reflected in sub-optimal neurological development, the extent of which will be reflected in the degree of motor deficit. The individual variability in the deficit is explained by the individual differences in the thyroxine production and other factors such as maternal-fetal competition for available iodine (6,40).

In a group of children aged 11 yr in 1978 and 15 yr in 1982, psychomotor performance was measured (Study 4) but no differences were found between children of mothers who received iodine during pregnancy and those of mothers who did not. Of a group of 208 children aged 6-12 yr, 115 were born to iodine-treated mothers and 79 to the saline group 14 of whom were cretins (25). The smaller number of children in the saline group was attributed to the high infant and child mortality rate in this group. The authors reported (Study 5) no difference between the two groups in grip strength or movement as measured by tapping and dotting and by nutting bolts. Although no differences were noted in gross motor skills, the treated group was better in pegboard and bead threading, indicating that finer motor tasks, demanding speed and accuracy, were improved in children born to iodine-sufficient mothers.

The series of intervention studies (Studies 6-9) was started in Ecuador in 1966 when the entire population of one village (Tokachi) was injected with iodized oil while a second village (La Esperanza) was kept as a control. Women of child-bearing age and children born since 1966 in the test village were re-injected in 1968. In 1968, a group of 6 - 10 yr-old children, injected with iodized oil in 1966 were compared with children from the control village using the Goodenough Draw-A-Man test (Study 6). The treated children had higher scores than did children from the control village but with a 2-sided Student's t-test, the difference was only significant for girls. Using a one-sided t-test, which could perhaps be justified if an improvement in performance was to be expected, the difference was significant for the whole group. The authors conclude that this could be due to the small sample and limited number of tests. However, the results are of considerable clinical significance as it indicates the possibility of correcting cerebral function in children living in endemic iodine-deficient areas as late as the age of 8 yr.

In one study (Study 7), the authors compared the mental development test scores between children who received iodine through the mother during the last phase of pregnancy, during lactation and also directly by intramuscular injection and children who received iodine through the mothers throughout the intra-uterine period, during lactation and directly by intra-muscular injection. These children were also compared with children of similar age/sex in control villages. The authors concluded that iodine prophylaxis early in fetal life prevented mental retardation while supplementation late in fetal life or after birth did not prevent mental retardation.

Trowbridge (Study 8) compared three groups of children in Tokachi (test village) according to the time of their conception with children in La Esperanza (control village). In the test village, Group 1 received iodine post-natally; Group 2 were born within 9 months of the start of iodine supplementation; while Group 3 were born 9 to 18 months after the iodized-oil campaign commenced. The scores of the three groups of children using a modified version of Stanford-Benit Intelligence test were compared among themselves and with scores of children from the control village in each group. There was no significant difference between the test and control villages on mean IQ score. However, in the test village, the IQs of children in Group 1 were lower than those in Group 2 and 3.

In 1981 Fierro-Benitez et al (Study 9) compared school performance of 128 children born to mothers injected with iodized-oil with 293 children born to control mothers. The authors found no difference in the age at admission to school. However, a higher percentage of children born to treated mothers were found to be in higher grades than children from control village indicating a higher repetition rate in control children: 64% failed at least once in the treated group compared to 80% in the control group. The authors also applied the Terman-Merrill, Bender-Gestalt, Wechsler Intelligence Scale for Children, Goodenough Draw-A-Man, Goddard and Raven color matrix tests to children of different age-groups. These tests measure verbal, numerical and spatial ability, immediate memory, verbal and numeral skills, perception, reasoning, visual memory, speed and accuracy. No statistically significant scores were obtained between the two groups in the Terman-Merrill, Wechsler and Goodenough tests. While the treated children scored higher in the Goddard and Bender-Gestalt tests, in the Raven children had lower scores than untreated children. The authors concluded that the lower scores of untreated children in the Goddard and Bender-Gestalt tests are an indication of the effect of delayed maturation of regions of the nervous system dealing with psychomotor development. It is thus clear that iodine deficiency is directly involved in the impairment of intellectual and neuromotor performance found in association with endemic goiter. In a paper discussing the population referred to in Study 9, Fierro-Binetz and colleagues (41) reported that, 21 years after the initial intervention commenced, children born to mothers injected with iodized oil were doing better generally in life having good jobs, good school records, and were able to migrate to urban areas while the less-gifted children, born to iodine-deficient mothers not treated with iodine remained in the countryside. These conclusions are somewhat subjective because getting a job, education performance, ability to migrate and social class involve complex social dynamics but do give an indication of the improvement in life which can come through supplementation of mothers with iodine.

In a case-control study in Chile (Study 10) in which school children (age not reported) with and without goiter were matched for age and sex, those children without goiter scored higher on various tests used. In addition, there was a positive correlation of iodine deficiency, as measured by goiter size and serum levels of T3 and T4, with IQ score using the Wechsler Intelligence Scale for Children and the Koppitz test. The children were similar in nutritional status as measured by height-for-age, weight-for-height and history of pre and post-natal illness. The authors concluded that a moderate prevalence of goiter alters IQ, suggesting that the deficit in IQ increases with increased severity of iodine deficiency. This conclusion was substantiated by the fact that the IQ of this group of children was not as low as that of children in more severe iodine-deficient areas. The study however, did not show any difference in visio-motor coordination between the goitrous and non-goitrous children. The authors suggested that visio-motor coordination would only be affected in areas of severe iodine deficiency.

In 1976, Bleichrodt and colleagues (Study 11) compared children aged 6 to 20 yr in an iodine-deficient village (n=106) and iodine-sufficient (n=139) in children aged 6-20 yr in Indonesia with similar social and economic backgrounds. They also examined children under the age of 12 yr in Spain in an iodine-deficient (n=162) and an iodine-sufficient area (n=193). From 18 different tests for general intelligence and motor skills, appropriate tests were chosen for different age categories. In Indonesia, the authors found no difference in general intelligence in the youngest age group while a significant difference was noted in non-intelligence tests such as concentration, perception and motor skills which are all independent of educational background. In Spain, in the iodine-deficient children <2.5 yr, mental development was lower but there was no difference in psychomotor development while for the 2.5-5 yr and 6-12 yr groups, both were lower.

In an intervention study in Spain (Study 12), children who received iodized oil in one village (n=103) were compared with untreated children in a village with children with similar educational and nutritional status as measured by height-for-weight (n=102). No differences were observed in mental and psychomotor performance between the two groups.

In an ecological study in China, Boyages et al (Study 13) compared the IQ scores of several groups (7-14 yr, 28-35 yr & 30-35 yr) from iodine-deficient and iodine-sufficient rural areas with urban controls. The lowest IQ scores were found in the population from the iodine-deficient rural area with the iodine-sufficient rural areas and urban controls being successively higher. In the iodine-deficient villages, the authors were able to link the low IQ scores with low audiometric ability and presence of abnormal neurological signs.

In a double-blind, case-control study (Study 14) in Ubangi, Zaire, Thilly and colleagues injected mothers with iodized oil and placebo between 1973 and 1977 and followed thyroid function, and psychomotor and somatic development. They reported lower birth weight and later psychomotor development in children under two years born to untreated mothers (42) as evaluated by the Brunet-Lezine scale. Thirty-six children born to treated mothers (n=339) and 39 children born to untreated mothers (n=332) were tested at age 4-9 months, 10-15 months and 16-23 months using the Brunet-Lezine scale (not all children were tested at all ages). The authors reported that development quotients of children from untreated mothers were consistently inferior to those from treated mothers (statistically significant for age 4-9 mo and for the group as a whole). Thus these data show that congenital hypothyroidism and decreased thyroid function in newborns in Ubangi was associated not only with increased incidence of cretinism but also with retarded psychomotor development.

Thilly and colleagues (43) also examined whether hypothyroidism in children can be prevented by correcting iodine deficiency during pregnancy in a study of 671 children aged 0 to 7 years, whose mothers were given either iodized oil or placebo during the fifth month of pregnancy. The concentrations of iodine in urine and of T4 in serum of children born to the mothers who received the placebo were low throughout indicating a high frequency of infantile hypothyroidism with about 10% showing clinical signs of hypothyroidism. Among the treated group children up to the age of 2 yr, only one case of clinical hypothyroidism was noted. Between the age of 2 and 4 yr, there was a gradual decrease in T4 levels to levels in children born to untreated mothers. Thilly et al (38) also reported that the magnitude of the thyroid anomalies observed in newborns was directly related to those of the mothers living in iodine-deficient areas. Thus they concluded that thyroid insufficiency in pregnancy in regions with severe endemic goiter can cause increased risk of hypothyroidism and associated psychomotor defects in new-borns. These findings are in contrast to those reported by Pharoah et al (24) and Fierro-Benitez et al (32) who showed that correction of iodine deficiency after the fifth month of pregnancy did not have any beneficial effects on newborns in terms of psychomotor development. Thilly and colleagues (40) attributed this inconsistency to other factors such as goitrogens in the diet.

Bautista et al carried out the first double-blind, placebo controlled intervention study in which children and not their mothers were dosed with iodine. In this study (Study 15) in Tiquipaya, Bolivia, they administered 460 mg of iodized oil orally (Ethiodol®) or its placebo to 200 school children aged 66-144 mo with goiter but no signs of protein-energy malnutrition. Urinary iodine concentration, thyroid size and height were measured and physical examinations made every six months. A full scale assessment including intelligence tests (Stanford-Binet and Bender-Gestalt) was repeated after 22 months. Higher urinary iodine concentration and decreased goiter sizes were found in both treated and control groups. There were no differences in mental development between the groups. Although the authors reported a correlation between goiter reduction and IQ scores this study did not answer the question, whether correction of iodine deficiency could improve intelligence. The authors suggested that the increase in iodine excretion among the control population could have been attributed to recycling of iodine but a study in Ecuador among people who refused iodine supplementation did not show any improvement in iodine status suggesting that this explanation is unlikely.

Ma and colleagues summarized 14 studies conducted in 13 different localities in China involving iodine-deficient and comparable iodine-sufficient areas (presented here as Study 16). These studies, which were based upon the Stanford-Binet and Wechsler tests, showed a considerably reduced IQ among iodine-deficient populations. Mild psychomotor defects and hearing impairment were also recorded in iodine-deficient populations.

The iodine intervention studies referred to above point to an effect of iodine deficiency on mental development through an effect of hypothyroidism on anatomical development. However, there may be additional mechanisms for the impairment of mental development through inadequate hearing which leads to late learning. Yan-You and Shu-Hua (44) reported that mean hearing levels of apparently normal children living in iodine-deficient areas were significantly lower than that of children living in iodine-sufficient areas. In a three-year follow-up of 7-11 yr old children, after the introduction of iodized salt, the hearing level of children improved from 17.4 to 8.16 dB, from 16.1 to 8.93 dB and from 12.0 to 7.27dB in three study areas: such hearing capacity was similar (7.5 dB) to that of children in non-endemic areas. An improvement in hearing levels was also reported by Post et al (45) in hypothyroid patients after treatment with thyroid hormones. Gosling et al (46) also attributed excess hearing defects to higher prevalence of iodine deficiency. It is thus possible that children with defective hearing may lag behind normal learning procedures and hence may be slower in mental development through slow learning and interaction.

In a study recently carried out by the authors in Malawi (Study 17), iodine supplementation to primary school children was found to have a marked significant impact on mental development as measured by verbal fluency, exclusion, visual memory, verbal meaning, quantity and closure. The effects were quite dramatic especially with respect to verbal fluency. If the effects observed (1.4 SD) were applied across the full range of mental development tests used in measuring IQ, the improvement observed would correspond to an increase in 21 points. The performance on physical and psychomotor tests were less dramatic with significant improvement being seen only for eye-hand coordination (as measured by the ball throwing exercise), hand grip and sitting/standing. No effects were observed in the tapping, balancing, peg-board and reaction task tests.

Evaluation of the evidence

The fact that deficiency of iodine affects mental and psychomotor development of children is no longer an issue. The data from Papua New Guinea, Zaire and Ecuador analyzed as cross-sectional and intervention studies, have proved that correction of iodine deficiency before or early in pregnancy improves mental and psychomotor performance of offspring. However, until the present work (Study 17), there was no clear evidence that supplementation of iodine-deficient children of pre-school and primary school children results in improvement in mental and psychomotor development. The results were either negative (Studies 7 & 12) or only of border-line significance (Study 6).

Iodine deficiency in the first trimester of pregnancy results in impaired development of the central nervous system. This is a period of time when the fetus is dependent on the mother for the supply of T4. Our knowledge on the nature of the impairment produced comes mainly from studies mainly in animals (5) and a limited number in humans (7). Lack of T4 during the first trimester results in smaller brain size. This is associated with fewer neurones which are also shorter in length. The effects of iodine deficiency later in fetal life and after birth are less clear.

The evidence is clear that frank cretinism cannot be fully reversed. However there are reports, mainly from China that treatment of cretins can result in some recovery in functions such as hearing, sexual prowess and reproductive performance. However from a public health point of view the question as to whether subtle damage produced by iodine deficiency, less than that required to produce cretinism, is reversible. The most likely effect of administering iodine to children would be to restore metabolic function. After birth, thyroid hormones have a role in growth in general and in regulating metabolic rate and temperature. The studies from China on cretins mentioned above, indicate that iodine has not only a metabolic effect but also an anatomical effect. Thus it could be expected that correction of iodine deficiency in children not so severely affected as cretins, may also result in correction of not only metabolic but also anatomical defects.

Because the recent study from Malawi (Study 17) is the first in which supplementation of children has lead to improvement in all aspects of mental development studied and in selected aspects of psychomotor development, there is a clear need for the study to be replicated. Such replication should take place in several settings with different levels of iodine deficiency and with different cultural backgrounds. In addition, clinical and experimental studies should be carried out to gain an insight into the mechanisms by which iodine deficiency reduces mental and psychomotor development.

The prime target for any iodine deficiency control programs should be women prior to pregnancy. If women are not reached prior to conception, their iodine deficiency should be treated as soon as possible. The finding that the mental and psychomotor performance of children can be influenced positively by increasing their iodine intake and status provides justification to extending iodine supplementation programs to children. Up until now, such justification has been limited to reduction in goiter prevalence and the idea that the iodine status, not only of women but also of children should be improved.

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CHAPTER 5

Forced expiratory lung function indices (FEV_1 and FVC) in rural Malawian schoolchildren aged 6-8 years

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Summary

The aim of the study was to develop appropriate lung function reference values for young Malawian school children. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and five anthropometric variables were measured in 1990 in 400 school children, aged 6-8 yr, of the Ngoni tribe in rural Malawi. After one year the measurements were repeated in 273 children. FVC and FEV_1 were highly correlated with standing height, weight, thoracic circumference and height-for-age. Height and age-adjusted FEV_1 and FVC were not related to height-for-age or weight-for-height. The variance in FEV_1 explained was 55% and 46% in boys and girls respectively based on standing height and age accounted and, when the other anthropometric variables measured were taken into account, the explained variance increased to 63% in boys and 57% in girls. Standing height and age accounted for 47% and 39% of the variance in FVC in boys and girls respectively and the explained variance increased to 51% in boys and to 42% in girls with the addition of the other variables. The regression coefficients with only height as independent variable, derived from data in 1990 were comparable with those from the 1991 data but the constant term differed, possibly because of a learning effect of the performance of lung function tests. Recommended regression equations for Malawian children, based only on height and age, are presented.

Introduction

Pulmonary function studies have been carried out in various populations to establish reference values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) from which normal values can be predicted according to gender, standing height and age (1). Such reference values of respiratory function have been shown to depend on the ethnic origin of the population (2-5), and are used to identify abnormal pulmonary function. The FEV_1 and FVC are the most common pulmonary function parameters for diagnosis of airways obstruction. Because of the increasing number of people with pulmonary obstructive diseases in Africa (6), it is useful to have population-specific FEV_1 and FVC references.

Available reference equations for African populations were mainly constructed from African populations living outside Africa [2-5,7], without distinguishing ethnic groups. The few reference equations for Africans living in Africa, are mainly based on adults (8-10) or adolescents (11,12). In children only a few studies have been done (13-15), of which one measured only peakflow (13). The largest study in this area was from Shamssain et al (15), who measured lung function of children aged 6 to 19 years with a height of more than 1.20 m. Since Malawian children are stunted with heights less than 1.00 m in many children aged 6 years, the reference values of Shamssain et al cannot be used in this population.

The aim of this study was to obtain reference values of FEV_1 and FVC for rural school children from the N'goni tribe in Malawi. This is the largest study of pulmonary function in rural African school children to be reported. To obtain consistency of the reference values, they were calculated twice, based on two sets of measurements with a gap of one year in the same population. Anthropometric parameters known to be related to lung function were measured to explain variance in lung function. Regression equations, which might best predict lung function in the study population are presented.

Subjects and methods

Subjects

Four hundred healthy school children aged 6-8 years from three primary schools in Ntcheu district (altitude 1200 m), Malawi, were selected for this study. All children belonged to the N'goni ethnic group. Each child was questioned and examined physically by one experienced Malawian Senior Clinical Officer before being enroled in the study. No children were excluded on medical grounds. Informed consent was obtained from the parents before the onset of the study.

Study design

Anthropometric data were recorded, and lung function tests were performed in October/December 1990 and October/November 1991. This project was part of a study to evaluate the effect of iodine and iron on physical, psychomotor and mental development, which will be reported elsewhere. No effects were found of iodine and or iron treatment on lung function and anthropometric parameters. This enabled us to use these parameters for longitudinal analysis of the whole group, without the necessity to distinguish treatment groups.

Anthropometric measurements

Height, weight, mid-upper arm circumference (MUAC), triceps, biceps, and subscapular and suprailiac skinfolds were measured in duplicate, with standard procedure (16,17), by one of the authors (RS) and trained field assistants. Results are expressed as the mean and, if two measurements differed by a predetermined amount, they were repeated. Height was measured to the nearest mm (Microtoise), weight to the nearest 0.1 kg using an electronic scale (Tefal), skinfolds to the nearest mm by Harpenden callipers (Holtain®, Wales) and MUAC to the nearest mm using a flexible steel tape. Subjects were considered stunted if their height-for-age was > 2 SD below the median of a reference population and a similar criteria based on weight-for-height was used for wasting (17). Chronic malnutrition is represented by stunting and acute malnutrition by wasting.

Lung function

FEV_1 and FVC were measured in one forced expiration preceded by a deep inspiration. The procedures used were according to the recommendations of the European Respiratory Society (18). Measurements were recorded using a calibrated Printer Spirometer II (Micro Medical Ltd, Kent, Great Britain; volume resolution 10 ml, volume range 0-10 litres, flow range 0.1-12 L/sec, accuracy 3%), with the subject sitting and not wearing a nose clip. At least three technically satisfactory measurements, as judged by the investigator, were performed. The measurement with the highest sum of FEV_1 and FVC was taken as the best. All measurements were done by one of two graduate students (PB,SV). The procedure was demonstrated and the instructions were translated into the local language, Chichewa, by a trained native speaker.

Data Analysis

To assess repeatability all parameters were measured again in duplicate in 40 subjects, within 14 days of the first measurements. The mean of the duplicates of the first measurement was compared with the mean of the duplicates of the second measurement. Repeatability of all anthropometry and lung function data were computed according to Bland and Altman (19).

Differences between boys and girls and between the baseline and follow-up data were tested using two sample t-test and paired t-test respectively. The relationships between FEV_1, FVC and anthropometric parameters were examined by gender-specific linear regression. Stepwise multiple regression analysis was used to assess the simultaneous effects of age, height, weight, MUAC, sum of skinfolds and thoracic circumference on lung function measures (model 1). Because of the small data range no logarithmic transformation was done, as recommended by Chinn and Rona (20). A second model was constructed in the same way, using only the variables that proved significant and relevant from the first model.

To compare the regression equations of the baseline and follow-up data, the linear regression equation with only height as independent variable was used. They were compared by calculating 95% confidence intervals for the difference between the slopes, the common slope and the vertical distance between the lines, according to Gardner and Altman (21). The regression equations of both baseline and follow-up were used to construct recommended regression equations for this population. Correlation coefficients were computed for the relationship between lung function and height-for-age and weight-for-height for the baseline data. This was repeated for lung function as a proportion of predicted values according to model 2 at baseline (height- and age-adjusted lung function).

Results

From 400 children full data sets were obtained at baseline. From 273 out of 400, at least lung function and height were obtained at follow-up. The 127 drop-outs did not differ significantly at baseline from the children who completed the study with respect to age, gender, anthropometric characteristics or lung function. On checking for reproducibility no significant differences were found between the first and second measurements, and the differences were not significantly correlated with the mean of two measurements. Reproducibility coefficients of FEV_1 and FVC were 0.15 and 0.25 respectively. About 27% of the children were stunted and 2% were wasted at baseline. Baseline values for anthropometric variables, FEV_1 and FVC are presented in Table 1. Since the values of FEV_1 and FVC were significantly higher in boys than in girls ($t=4.48$, $df=389$, $p<0.001$), the data from the boys and girls were not pooled.

All anthropometric parameters were positively correlated with the FEV_1 and FVC except for sum of four skinfolds, which was negatively correlated with FEV_1 and FVC. In multiple regression analysis, besides standing height and age, addition of other anthropometric variables increased the explained variance in the FEV_1 (FVC) significantly from 55% (47%) to 63% (51%) in boys (Table 2). The corresponding values for girls were 46% (39%) to 57% (42%) respectively. The parameters that significantly caused this improvement differed between the FEV_1 and FVC and between boys and girls.

For FEV_1 and FVC the slopes of the regression equations with height as independent variable did not differ significantly between the baseline and final measurement. However a significant vertical difference between the baseline and follow-up regression equations was found for both sexes. This means that for a given height, FEV_1 and FVC were significantly higher at the follow-up. For this reason and reasons of

Table 1 **Anthropometric parameters and lung function, FEV_1 and FVC in children at baseline***

	Boys n=210	Girls n=190
Age yr	7.1	7.1
Standing height cm	116.6 (7.3)	115.8 (6.3)
Weight kg	20.8 (3.2)	20.3 (2.8)
Thoracic circumference cm	58.6 (3.0)	57.8 (3.3)
MUAC cm	16.8 (1.2)	17.0 (1.2)
Sum of 4 skinfolds mm	18.8 (4.1)	21.8 (5.4)
FEV_1 L	1.01 (0.23)	0.92 (0.20)
FVC L	1.16 (0.31)	1.03 (0.26)

* Mean±SD.

consistency, regression equations with only height and age are used in the second model. Height-for-age was significantly ($P<0.001$) correlated with FEV_1 and FVC in a positive mode, with correlation coefficients of 0.55 and 0.45 for FEV_1 in boys and girls respectively, and of 0.48 and 0.41 for FVC in boys and girls respectively. Weight-for-height did not correlate with lung function. When FEV_1 and FVC were calculated as a percentage of predicted, according to model 2 at baseline, they both did not correlate with height-for-age and weight-for-height.

Discussion

This report presents the largest study of southern African rural school children aged 6-8 yr. The present finding shows that prediction of lung function for Malawian populations becomes more appropriate by entering more specific anthropometric variables into the gender-specific linear regression equations. However, we recommend regression equations with only height and age, for the following reasons. Firstly, the parameters that significantly caused this improvement of explained variance differed between the FEV_1 and FVC and between the genders. For example thoracic circumference significantly contributed to the explained variance of FVC in boys but not in girls. Thus, it was not possible to add one consistent parameter to the regression equations. Secondly, it would be too complicated to measure all these parameters in everyday practice. Finally, although age does not significantly contribute to the explained variance, because of the narrow age range, it is included in our regression equations in order to be able to compare it with other studies.

Table 2 **Multiple regression coefficients for FEV_1 and FVC using different parameters as explanatory variables, at baseline and follow-up**

Explanatory variables	Sex	MODEL 1 Baseline n=198M, 186F	MODEL 1 Follow-up n=135M, 111F	MODEL 2 Baseline n=210M, 190F	MODEL 2 Follow-up n=148M, 125F
FEV_1					
Age yr	M	0.007 (0.015)	0.010 (0.018)	0.017 (0.015)	0.029 (0.018)
	F	0.017 (0.015)	0.002 (0.022)	0.025 (0.015)	0.004 (0.020)
Height cm	M	0.011 (0.003)†	0.013 (0.005)*	0.021 (0.002)†	0.024 (0.002)†
	F	0.014 (0.003)†	0.018 (0.007)†	0.020 (0.002)†	0.022 (0.003)†
Thoracic circumference (cm)	M	0.024 (0.005)†	0.026 (0.009)†		
	F	0.013 (0.005)†	0.019 (0.012)		
Weight kg	M	0.013 (0.007)	0.015 (0.018)		
	F	0.009 (0.009)	-0.006 (0.021)		
MUAC (cm)	M	-0.008 (0.012)	0.002 (0.023)		
	F	-0.012 (0.014)	0.017 (0.023)		
Sum of four skinfolds (mm)	M	-0.007 (0.003)*	-0.009 (0.005)		
	F	-0.006 (0.002)*	-0.005 (0.005)		
Constant	M	-1.709 (0.310)†	-2.119 (0.743)	-1.601 (0.178)†	-1.982 (0.244)†
	F	-1.382 (0.372)†	-2.260 (0.901)	-1.573 (0.207)†	-1.645 (0.309)†
Residual SD	M	0.15	0.15	0.16	0.16
	F	0.14	0.15	0.15	0.17
Explained variance	M	0.57	0.62	0.51	0.55
	F	0.50	0.48	0.44	0.39
FVC					
Age yr	M	0.011 (0.023)	0.001 (0.025)	0.029 (0.023)	0.024 (0.025)
	F	0.025 (0.021)	0.028 (0.025)	0.033 (0.021)	0.040 (0.025)
Height cm	M	0.012 (0.004)†	0.018 (0.007)*	0.026 (0.003)†	0.031 (0.003)†
	F	0.016 (0.005)†	0.012 (0.008)	0.023 (0.003)†	0.023 (0.003)†
Thoracic circumference (cm)	M	0.030 (0.008)†	0.033 (0.013)*		
	F	0.009 (0.007)	0.010 (0.013)		
Weight kg	M	0.019 (0.011)	0.015 (0.024)		
	F	0.017 (0.013)	0.024 (0.024)		
MUAC cm	M	-0.008 (0.019)	-0.007 (0.031)		
	F	-0.011 (0.020)	0.004 (0.026)		
Sum of four skinfolds (mm)	M	-0.009 (0.004)*	-0.011 (0.007)		
	F	-0.007 (0.003)*	-0.010 (0.005)		
Constant	M	-2.133 (0.477)†	-2.709 (1.020)†	-2.087 (0.267)†	-2.516 (0.239)†
	F	-1.493 (0.514)†	-1.387 (1.025)	-1.916 (0.284)†	-1.790 (0.372)†
Residual SD	M	0.23	0.20	0.24	0.22
	F	0.20	0.17	0.21	0.20
Explained variance	M	0.46	0.56	0.42	0.51
	F	0.42	0.50	0.37	0.36

Model 1: using all parameters; model 2: using only age and height
The values in brackets represent standard errors of the regression coefficients
MUAC; mid upper arm circumference; * $P<0.05$; † $p<0.01$

When regression equations based on Caucasian populations are used in an African population such as in the present study, predicted values may be overestimated (1). For example, the mean FEV_1 in N'goni boys and girls was only 85% and 82% of predicted value for boys and girls of Zapletal's data (22). In addition differences in body build, genetic constitution and environmental exposure may play a role in such differences.

The explained variance of the regression equations was smaller than previously reported (1,3,4,9,11,15). A possible explanation for this difference could be the lack of information on past respiratory infections. Even though the children enrolled in the study were clinically healthy, many of them may have had latent infections or a history of illness including acute respiratory infections, which could have negatively influenced their lung function (23). Other possible factors which could contribute to increasing the explained variance in FEV_1 include the amount and nature of household air pollution arising from open fires used for heating and cooking and the preparation of food. However no attempt was made to measure such pollution because of the difficulties in estimating the degree of exposure of individual children to such pollutants. Reproducibility of the measured parameters is considered not to influence the explained variance.

Weight-for-height and height-for-age were not entered in the equations as height, age and weight were entered separately. Our results show that, although height-for-age highly correlates with lung function, stunting does not affect the height- and age-adjusted FEV_1 and FVC. Very little is known about the effects of malnutrition on lung growth and lung function (24). It has been reported previously that wasting affects height-adjusted peak flow rate but stunting does not (25). This cannot be confirmed for FEV_1 and FVC in this study, as only 2% of the children were wasted.

The difference between baseline and follow-up in the constant factor of the regression equations can be explained by several factors including a possible learning effect (7). At baseline, the children had never experienced a spirometer before and they might have had to get used to it. However, this was not confirmed by calculating reproducibility, as estimated by two measurements, with two weeks in between. Secondly past events may have affected lung function, such as respiratory infections, for example tuberculosis (23,26). These events can result in growth retardation of the lungs at that time, but do not necessarily affect the lung growth afterwards. This argument was used to explain a difference in the annual decrease in lung function between longitudinal and cross-sectional analysis in adults (27,28). Our results show the same effect on lung function increase in children. Another possibility is that the linear regression equations, that were used because of the narrow range of the parameters within the study population, should in fact be exponential. We consider the possibility of a cohort effect

Table 3 **Recommended regression equations for FEV_1 and FVC for N'goni children aged 6 to 8 years**

Regression equation			Residual SD
Boys			
FEV_1 (L)	=	0.022 * height (cm) + 0.023 * age (yr) - 1.78	0.16
FVC (L)	=	0.028 * height (cm) + 0.027 * age (yr) - 2.30	0.23
Girls			
FEV_1 (L)	=	0.021 * height (cm) + 0.015 * age (yr) - 1.61	0.16
FVC (L)	=	0.023 * height (cm) + 0.036 * age (yr) - 1.85	0.21

not likely. A bias by drop-outs was ruled out, because no differences were found between the drop-outs and the children who completed the study.

It can be concluded that lung function of stunted children should not be compared to reference equations for normally nourished children. The reference equations presented here are more appropriate for stunted children. The calculated reference equations can vary between years within a study population. This indicates that cross-sectional regression equations should not be used for describing longitudinal changes. It is difficult to choose which of the equations presented in the results predicts most accurately the lung function in N'goni children aged 6 to 8 years. Considering all factors mentioned above, we recommend regression equations as presented in Table 3, based on the model 2 of baseline and follow up observations.

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CHAPTER 6

General Discussion

Background

Almost one billion people in the world are estimated to be at the risk of iodine deficiency disorders. The growing understanding on the relationship between iodine status and the overall integrity of human behaviour has directed the spotlight on iodine deficiency. The fact that a large proportion of apparently normal populations, living in iodine-deficient environments may develop varying degrees of mental deficiency has become a cause of concern for all. Various studies using iodized oil, administered orally or by intramuscular injection, or iodized salt have shown different degrees of success in controlling iodine deficiencies as measured by reduction in prevalence of goiter and of endemic cretinism. Virtual elimination of iodine deficiency by the year 2000 has been set as a global target by UN agencies. UNICEF has brought this target forward by five years.

It is estimated that over half of the children and women in developing countries suffer from iron deficiency and the prevalence in developed countries is also a cause for concern. The etiology of iron deficiency can be viewed as a negative balance between iron intake and iron loss. During the period of rapid growth such as in infancy and early childhood, blood volume expands in parallel with physical growth, with a corresponding increase in iron requirements which are not usually met from a child's diet in developing countries. In several studies, children with iron-deficiency anemia consistently scored lower in various mental and psychomotor development tests compared with iron-sufficient children.

The etiology of iodine deficiency and of iron deficiency are unrelated but occur together in many developing countries. Both deficiencies are related to food intake. It is therefore not surprising that these problems are common more often in economically depressed areas. How do the combined deficiencies affect a population? And how does combined supplementation affect overall physiological and psychological integrity of human individuals? These are the questions that demands the skills of psychologists, epidemiologists, and those involved in program planning and implementation at the national and international level.

In the absence of population-specific data, it is difficult to estimate with any accuracy the number of people affected by iodine and iron deficiencies in Malawi. Based upon surveys in eight districts, the Ministry of Health estimated that 1.5 to 2.5 million people are living in an iodine-deficient environment of whom about 500,000 people were goitrous.

No nationwide data on iron deficiency anemia are available. According to the Annual Reports of the Ministry of Health, more than 40% of women of childbearing age suffer from iron-deficiency anemia. No specific data on children were available but, considering the high rates of malnutrition in children and the high prevalence of anemia in women, it is likely that a high prevalence of anemia also exists among children. In Malawi, like in many other developing countries where adverse health conditions such as malaria and intestinal parasitic infestations are common, the consequences of iron deficiency anaemia become severe.

In most developing countries including Malawi, the consumption of animal products is low and is unlikely to increase due to economic reasons. Similarly the universal availability of iodized salt is also hindered by the trade policies which makes iodized table salt often more expensive than sugar. The current situation with respect to iodine and iron deficiencies are thus, likely to continue until a long term supply of iodized salt and iron fortified staples become an everyday reality.

A study on the quality of primary school education in Malawi in 1987 indicated that only a small proportion of total Government funds were allocated to the education sector. Again the largest share of this budget goes to paying salaries and providing physical facilities at the expense of teaching materials and the development of human resources. Only about 40% of primary school age children have access to primary schools. Further, only about 30% of girls have ever been enrolled in primary school. Of the total school enrolment, between 30 and 40% drop out during the first year of schooling. As a result of the high rate of dropout and of repeating classes, it takes those who complete primary school in Malawi an average of 17 years.

This study

It is against this background that children learn in Malawi. Evaluation of school learning was not the objective of the present study but, within this framework of learning, two main questions were addressed. Firstly, how does deficiency of iodine and of iron affect mental and psychomotor development of Malawian primary school children? Does supplementation with iodine and/or iron help children to improve their mental and psychomotor ability? A double-blind, placebo-controlled trial in which children were supplemented with iodine and/or iron was implemented to address these questions.

In **Chapter 1** the role of iodine and iron is briefly reviewed in relation to the prevailing conditions of micronutrient malnutrition and manifestation of the deficiencies of iodine and iron, such as goiter, cretinism and cognitive development. A brief overview of the present study is also outlined in this section. Based upon the intervention of this study the results of the effect of iodine and/iron supplementation on physical and psychomotor development tests are presented in **Chapter 2**. The iodine and/or iron supplementation did not show any impact on the physical growth of children. Iodine supplementation however, had a strong positive impact on physical stamina as measured by hand grip and sitting standing abilities. Iron supplementation also improved eye-hand coordination. Psychomotor tasks, demanding speed and perseverance were not affected by iodine and/or iron supplementation. Overall the results of treatment on physical and psychomotor development were less dramatic than on mental development.

The findings on a range of mental development are described in **Chapter 3**. The tests used were chosen in order to measure long term memory, recollection, visual memory, figural relationship, vocabulary, concept development, comprehension, perceptual speed, reasoning and reconstruction skills. All these skills are essential for classroom learning. The study found a positive effect of iodine supplementation on all of the parameters measured while the effect of iron supplementation was more limited. With the study design, it was possible to measure the effect of the interventions with the tests used. The tests could also be applied to detect children in Malawi with learning difficulties. However the results from these tests should not be used for inter-country comparisons because of their *cultural insensitivity*. The closure tests was found to be most difficult by the children perhaps reflecting the general atmosphere in which the children are growing up. Perhaps it is an environment where children are not exposed to opportunities for challenging their mental abilities with respect to the perception of things and events. More studies will be needed to test this finding.

In **Chapter 4** previous studies on iodine supplementation and its impact on mental and psychomotor development were reviewed. Manifestations of the effects of iodine deficiency on the human body such as goiter, hypothyroidism, cretinism and reproductive failure are briefly described. The role of iodine and thyroid gland during fetal development is briefly reviewed. The role of various iodine and non-iodine factors in relation to mental development of children are also briefly highlighted. The available literature indicate that iodine status before and during pregnancy is critical for mental development of offspring. If the fetus is supplied with enough iodine during pregnancy the brain and central nervous system of child develops normally. Whereas if the iodine supply is inadequate during the fetal stage, brain and central nervous system damage appear to be irreversible depending upon the level of iodine deficiency and the extent of damage.

Extrapolating the data available from other countries on micronutrient deficiencies and superimposing them on Malawi, it is estimated that annually 57,000 student-years are lost due to learning difficulties; 213,000 person-years of work are lost; 3,300 preventible deaths occur and 1,800 children are handicapped. Such a scourge could be substantially reduced. There is no natural hunger for iodine or iron. As a result there is a lack of consumer awareness regarding the need for iodine and iron. The advocacy by the international agencies is changing this situation but a constant vigilance to monitor the level of intake and new ways of getting iodine to the people must be continually explored.

The present study showed a differential effect of iodine and iron supplementation on physical, psychomotor and mental development. Based upon the results of this study, supplementation with iodine was found to be more effective than iron in improving mental development. Within the sphere of mental development, fluid intelligence was much more strongly affected than crystallized intelligence and perceptual skills of children by such supplementation. In addition there appear to be no interaction between iodine and iron supplements. Overall the supplementation with iodine improved mental development score of children by 21 points (1.4 SD) on a standardized scale.

This is the first time that a clear positive effect of iodine supplementation on the mental development of children has been observed. Positive effects of supplementation with iodine during or before pregnancy have been demonstrated before on several occassions both in humans and in animals. The results of post-natal supplementation with iodine had been inconclusive due to various reasons such as a wide range of age groups of the sample population, sample size, number of tests used and possibly to a learning effect associated with administering the tests often as many studies were done on the same populations over a period of time.

This study also looked at the pulmonary function of children with respect to iodine and iron supplementation. Previous studies had shown hypoventilation in myxedematous condition leading to pulmonary failure. This study did not find any improvement in lung function as a result of iodine and/or iron supplementation.

There was excellent compliance with regards to dosing with oral iodized oil. However, additional work needs to be done to examine alternative oral dosing methods and on factors affecting the retention of iodine. Further, this study should be replicated in different cultural setting, perhaps using the same research instruments, in school-going and non-school-going populations, to verify the present findings.

Conclusions and recommendations

1. Four hundred and twenty-four children in Ntcheu District in Malawi were enrolled in this placebo-controlled double-blind trial in which a single dose of iodized oil and daily doses of iron were given. The children, aged 6-8 yr, were from Standards 1 and 2 of Lizulu, Mlanda and Chirobwe primary schools. The family background and the characteristics of children in the four groups were similar at the beginning of the study. Complete sets of data were obtained from 241-321 children.

2. About 86% of the study population were moderately iodine deficient at baseline with urinary iodine concentrations below 0.4 μmol/L, while 18% were anemic with blood hemoglobin levels below 110 g/L. About 27% of the study population were stunted and 2% were wasted.

3. Seven tests of psychomotor development and seven tests of mental development were chosen for the present study. These culture-reduced tests, previously used in a variety of cultural settings, were pretested in a separate village and found to be suitable for the study. The tests were conducted by specially-trained field-workers, who spoke the same language as the subjects (Chechewa), under close supervision.

4. After the baseline measurements were made, the children were supplemented with iodine and daily supplementation with iron was commenced. The oral administration of iodine with a dispenser was convenient and no child refused the dose. The concentration of iodine in urine was found to be increased when measured after 3 months but had returned to baseline when measured after one year. This would indicate that the dose used (1mL Lipiodol® UF) was inadequate to maintain urinary iodine levels at a satisfactory level for a period of one year. The iron supplement (ferrous sulphate, 60 mg Fe) was administered daily (Monday-Friday) during school term by the headmasters of the three schools. It was not possible to monitor blood hemoglobin levels after dosing had commenced because of objections from parents in obtaining further blood samples.

5. All subjects were found to be taller and heavier one year after the baseline measurements but there were no differences at this time among the four treatment groups in any of the anthropometric parameters measured. Thus neither iodine nor iron supplementation had any effect on physical growth of the children.

6. In this study, supplementation with iodine was found to influence strongly fluid intelligence (recall memory, verbal tasks and recognition), crystallized intelligence (information processing and word meaning) and perceptual skills (figural units, and comparison and extraction of information). Supplementation with iron improved

fluid intelligence but did not influence the other two components of mental development. If the effects observed extended over the entire range of mental development tests, the impact of iodine supplementation would correspond to an improvement in IQ of 21 points (1.4 SD). This study has demonstrated for the first time that supplementation of children with iodine as late as at primary school age can have a positive impact on mental development. Most previous studies had been directed towards iodine supplementation of women before or during pregnancy.

7. Over the period of the study, psychomotor performance of all children improved indicating maturation of various psychomotor functions. Iodine supplementation improved psychomotor performance with respect to eye-hand coordination and physical stamina while only eye-hand coordination improved with iron supplementation. Neither iodine nor iron supplementation improved speed or dexterity.

8. Thus supplementation with iodine was found to have a strong positive impact on mental and psychomotor development of children while the effect of iron was less marked. There was no interaction between supplementation with iodine and iron.

9. This study confirms the beneficial effects of increasing the supply of iron to children on their mental development.

10. This is the first study to demonstrate the effectiveness of iodine supplementation to children in improving mental and some aspects of psychomotor development. Thus, it should be replicated in a number of areas differing in cultural background and severity of iodine deficiency.

11. Iodination of salt has proved to be a successful method of providing iodine to populations in many countries. The cost of iodination, estimated at US$ 5 to US$10 per ton depending upon the local situation, is reasonable. In landlocked countries without local salt production, provision of iodized salt can present problems. For example in Malawi, the price of iodized table salt was often higher than that of sugar while in Nepal, the cost of transporting salt to at-risk areas was often more than US$ 1 per kg. However, the problems involved in salt iodination programs can be overcome provided there is political will and adequate financial resources.

12. Until iodized salt becomes readily available, oral dosing with iodized oil is an effective method which should be used for population groups particularly at risk of iodine deficiency. This study has shown that primary schools are an effective means of treating a large number of children but alternative ways will need to be used to reach other sectors of the population.

Summary

Primary school children (n = 424) from the Ntcheu District, Malawi, aged 6 - 8 years, were selected for a double-blind placebo-controlled study to evaluate the effect of iodine and iron supplementation on physical, psychomotor and mental development. After the baseline measurements were carried out, children were given a single dose of iodized oil (1 mL Lipiodol®; 490 mg I) or placebo and daily doses of iron (ferrous sulphate, 60 mg of Fe) or placebo on weekdays (February-July and October-November 1991).

The anthropometric measurements included height, weight, mid-upper arm cicumference (MUAC), and four skinfolds while indicators of physical stamina included lung function, hand grip and sitting and standing ability. The psychomotor development tests were pegboard, ball throwing, tapping and reaction time tasks. The mental development tests included fluency and exclusion as a measure of fluid intelligence; quantity and verbal meaning to evaluate crystallized intelligence and visual memory and closure tests to measure perceptual skills. Baseline data were collected from October 1990 to January 1991 and the final tests and measurements were carried out in October-November 1991.

The initial iodine and iron status was established by measuring the concentration of iodine in urine and of hemoglobin in blood. About 86% of children had urinary iodine concentrations below 0.4μmol/L indicating moderate iodine deficiency while 18% of children had hemoglobin levels below 110 g/L which is the cut-off point for indicating anemia. Measurement of iodine in urine three months after supplementation showed a normal level of urinary iodine. After one year, the level had dropped to the baseline value. The change in haemoglobin could not be measured due to objections from the parents in obtaining further blood samples. About 27% of children were stunted while 2% were wasted when measured at both time points.

One year after supplementation, the four treatment groups did not grow differentially indicating no effect of iodine or iron supplementation on physical growth. The iodine-treated group scored higher in tests of physical stamina as measured by sitting-standing and hand grip. The iodine treated group also significantly improved scores on the ball throwing exercise indicating an improvement in eye-hand coordination. No changes were noticed on reaction time, movement time and tapping indicating no effect of iodine on speed, dexterity and manual-motor coordination. The iron-treated group showed improvement only in eye-hand coordination tests. No improvements were seen in other psychomotor tests.

Subjects in all four groups improved their scores on all mental development tests. The analysis of the placebo group indicated a considerable learning effect especially in

fluency. Detailed analysis were conducted based upon the differential improvement when compared with the placebo group during the final test. The iodine-treated groups showed a large improvement in fluid intelligence measured by the fluency and exclusion tests. This component of intelligence measures reasoning, classification and fluency. Perceptual skills, as measured by visual memory and closure, also improved considerably in the iodine-treated group. Crystallized intelligence, as measured by quantity and verbal meaning, was also improved in the iodine-treated group but to a lesser extent than fluid intelligence. Crystallized intelligence is associated with word meaning, factual knowledge, short term-memory and decision making. These skills are closely associated with the classroom environment.

In the iron-treated group, a significant improvement was noted only in fluid intelligence and in the quantity test, a component of crystallized intelligence. No significant interaction of iodine and iron was noted. However, combined supplementation with iodine and iron sometimes resulted in an additive effect.

It has been shown in several studies in which iodine has been administered to mothers prior to pregnancy or during gestation that iodine supplementation reduces spontaneous abortion and stillbirths and improves the birth weight, and the mental and psychomotor performance of children. Previous studies in which children have been supplemented with iodine have not been able to demonstrate unequivocally that such supplementation affects mental or psychomotor development. In the present study we were able to demonstrate that iodine supplementation to children as old as 6-8 yr could improve mental and psychomotor development. The present study also demonstrates that iodine supplementation was more effective than iron supplementation in the population studied but the low prevalence of iron-deficiency anemia in children could have been responsible for such an outcome.

Concerning supplementation with iron, several previous studies have indicated that correction of iron deficiency early in infancy tends to improve psychomotor and mental development more than when the correction takes place in later life. In the present study, supplementation with iron was found to improve eye-hand coordination and fluid intelligence which justify prevention and control of iron-deficiency anemia in infants and children as soon as such a problem is detected.

An important finding from the perspective of planners is that 490 mg oral iodine may be inadequate to provide sufficient iodine for one year as indicated by the measurement of urinary iodine excretion. In iodine-deficient areas where provision of iodized salt is not available, the provision of iodized oil capsules could be an attractive alternative provided that the dosing schedule is adequate.

Samenvatting

Een dubbel-blind placebo-gecontroleerd onderzoek naar de effecten van jodium en ijzer supplementatie op fysieke, psychomotorische en mentale ontwikkeling werd uitgevoerd onder lagere school kinderen (n=424, 6-8 jaar oud) afkomstig uit Ntcheu District, Malawi. Nadat basis gegevens waren verzameld, werd de kinderen een eenmalige dosis gejodeerde olie (1 mL Lipiodol®; 490 mg I) of een placebo en een dagelijkse dosis ijzersulfaat (60 mg Fe) of een placebo op elke weekdag gegeven. De antropometrische metingen omvatten lengte, gewicht, armomtrek en vier huidplooien. Indicatoren voor fysiek uithoudingsvermogen waren longfunctie, handkracht en vaardigheid in zitten en staan. De psychomotorische testen bestonden uit pennenbord, balwerpen, aantikken en reactie tijd testen. De testen gebruikt ter meting van mentale ontwikkeling waren verbale vlotheid en exclusie als maat voor 'fluid intelligence', inschatting van afmeting en invulling ter evaluatie van 'crystallized intelligence' en verbale en visuele geheugen testen ter meting van perceptuele vaardigheden. Basis gegevens werden verzameld van oktober 1990 tot januari 1991 en de eind testen en metingen werden uitgevoerd in oktober-november 1991.

De jodium en ijzer status werden aan het begin vastgesteld aan de hand van jodium concentratie in de urine en hemoglobine gehalte van het bloed. Ongeveer 86% van de kinderen had een jodium concentratie in de urine onder 0.4 μmol/L welk niveau een gematigde jodium deficiëntie aangeeft. Daarnaast had 18% een hemoglobine gehalte onder 110 g/L welk niveau anemie aangeeft. Jodium concentratie in de urine, gemeten drie maanden na supplementatie, had een normaal niveau. Eén jaar na supplementatie was de jodium concentratie weer gedaald tot het begin niveau. De verandering in hemoglobine gehalte kon niet gemeten worden vanwege bezwaren van de ouders tegen bloed afname bij hun kinderen. Ongeveer 27% van de kinderen was te klein voor hun leeftijd ('stunted') en 2% was te licht voor hun lengte ('wasted') tijdens beide meetpunten.

Eén jaar na supplementatie werden er geen verschillen in groei gevonden tussen de vier behandelingsgroepen. Dit wijst erop dat jodium of ijzer supplementatie geen effect heeft op fysieke groei. De groep behandeld met jodium scoorde hoger bij fysieke vaardigheidstesten zoals gemeten via zitten en opstaan en handkracht. Deze groep vertoonde ook een significante verbetering in scores met betrekking tot balwerpen, wat een verbetering in de oog-hand coördinatie aangeeft. Geen veranderingen werden waargenomen in reactie tijd, bewegingstijd en aantikken: dit geeft aan dat jodium geen effect heeft op snelheid, behendigheid en handvaardigheid coördinatie. De groep behandeld met ijzer vertoonde slechts een verbetering in oog-hand coördinatie testen. Geen verbeteringen werden gevonden in andere psychomotorische testen.

De kinderen in alle vier de groepen verbeterde hun scores bij alle mentale ontwikkelingstesten. De analyse van de placebo groep wees op een aanzienlijk leereffect

met name in vlotheid. Een gedetailleerde analyse was gebaseerd op de differentiële verbeteringen vergeleken met de placebo groep tijdens de eind testen. De groepen behandeld met jodium vertoonden een grote verbetering in 'fluid intelligence' zoals gemeten door vlotheid en exclusie testen. Deze component van intelligentie meet argumentatie vaardigheid, categorisrering en vlotheid. De perceptuele vaardigheden, gemeten via visueel geheugen en invulling, verbeterden ook aanzienlijk in de groep behandeld met jodium. 'Crystallized intelligence', gemeten door inschatting van afmeting en verbale betekenis, verbeterde ook in de jodium groep, maar in mindere mate dan de 'fluid intelligence'. 'Crystallized intelligence' is geassocieerd met woord betekenis, feitenkennis, korte termijn geheugen en besluitvorming. Deze vaardigheden zijn nauw verbonden met de leeromgeving. In de groep behandeld met ijzer werd alleen een significante verbetering gevonden in 'fluid intelligence' en in de hoeveelheid test, een component van 'crystallized intelligence. Er was geen significante interactie tussen ijzer en jodium. Een gecombineerde supplementatie van ijzer en jodium resulteerde echter in enkele gevallen in een additief effect.

Verscheidene studies, waarin jodium werd toegediend aan moeders voor en tijdens de zwangerschap, hebben aangetoond dat jodium supplementatie het aantal spontane abortusgevallen en het aantal doodgeborenen vermindert en het geboortegewicht en mentale en psychomotorische ontwikkeling van kinderen verbetert. Eerdere studies waarin kinderen jodium supplementen waren gegeven, konden niet eenduidig aantonen dat een dergelijke supplementatie effect had op mentale en psychomotorische ontwikkeling. In deze studie hebben we aangetoond dat jodium supplementatie bij kinderen van 6 tot 8 jaar oud een verbetering in mentale en psychomotorische ontwikkeling tot gevolg heeft. Deze studie toonde ook aan dat in de onderzoekspopulatie jodium supplementatie effectiever was dan ijzer supplementatie. Echter de lage prevalentie van ijzer deficiëntie bij de kinderen is mogelijkerwijs de oorzaak van dit resultaat.

Betreffende supplementatie van ijzer hebben verscheidene voorgaande studies aangetoond dat een correctie van ijzer deficiëntie op vroege leeftijd een grotere verbetering van psychomotorische en mentale ontwikkeling tot gevolg lijkt te hebben dan een correctie op latere leeftijd. In deze studie verbeterde ijzer supplementatie de oog-hand coördinatie en 'fluid intelligence'. Dit rechtvaardigt preventie en controle van ijzer deficiëntie anemie bij zuigelingen en kinderen zodra het probleem is vastgesteld.

Een belangrijk resultaat vanuit het oogpunt van planners is dat een orale toediening van 490 mg jodium onvoldoende zou kunnen zijn om voldoende jodium te leveren voor een jaar zoals aangetoond door de metingen van jodium excretie in de urine. In jodium deficiëntie gebieden waar gejodeerd zout niet beschikbaar is, zou de verschaffing van gejodeerde olie capsules een aantrekkelijk alternatief kunnen zijn mits het doseer regime toereikend is.

Curriculum vitae

Ramesh Man Shrestha was born on 18th November 1953 in Kathmandu, Nepal. He completed his undergraduate studies in Chemistry and Biology at Tribhuvan University in Kathmandu in 1971. He then undertook the program for the degree of Masters of Science in Human Biology and Anthropology at Punjab University in India graduating in 1973. After serving in the Institute of Medicine in Kathmandu as Research Officer from 1974 to 1979, he joined the International School of Public Health, Hebrew University of Jerusalem in 1980 where he completed his Masters of Public Health degree.

Ramesh worked as Programme Officer for Health and Nutrition in UNICEF Nepal from July 1982 to December 1985. In January 1986 he was transferred to UNICEF Malawi, as Head of Health Programmes until May 1991 when he was reassigned to the UNICEF office in the Socialist Republic of Vietnam as Programme Officer for Early Childhood Development. In April 1994, he will be taking up a new assignment as Assistant Representative in UNICEF Male, Maldives.

The work leading to this thesis was initiated in Malawi in January 1990 and extended to December 1991. The preparatory and the final phases of this research were carried out in the Department of Human Nutrition, Wageningen Agricultural University in 1990 and 1993-1994 respectively.

He is married with two children.