FUNCTIONAL CONSEQUENCES OF IRON DEFICIENCY

IN CHINESE FEMALE WORKERS

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Humane Voeding

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IN CHINESE FEMALE WORKERS

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THEOREMS

I

The apparent paradox of a high prevalence of nutritional iron deficiency in Chinese female workers with 'high' iron intake could be due to poor bio-availability of iron in the diet, high iron requirement in women using IUDs or an overestimation of iron contents in the Chinese food composition table used. (this thesis)

II

It needs to be stressed that even in the same individual, the calibration procedure should be repeated on different occasions in order to estimate individual energy expenditure from heart rate recording.(this thesis)

III

Reduced energy expenditure during work may make workers accomplish their tasks without undue fatigue, so that at the end of working days, they are left with sufficient vigour to enjoy their leisure time and perform their social duties.(this thesis)

IV

The amounts of menstrual blood lost in women are mainly genetically controlled. The main known external causes of variation in the amount of menstrual blood loss are anovulatory drugs, which reduce the blood losses by half and intrauterine devices, which double the losses. (L. Hallberg et al., Am J Clin Nutr 1991;54:1047-58)

V

Fluctuations in body weight may have negative health consequences, independent of obesity and the trend of body weight over time. (L. Lissner et al., N Engl J Med 1991;324:1839-44)

VI

The failure of some obese subjects to lose weight while eating a diet they report as low in calories is due to an energy intake substantially higher than reported and an overestimation of physical activity, and not to an abnormality in thermogenesis. (S.W. Lichtman et al., N Engl J Med 1992;327:1893-98)

VII

It seems that exclusive butter users eat what they like whereas margarine users like what they eat. (R. Prättäla et al., Appetite 1992;18:185-191)

VIII

Preterm babies whose mothers provided breast milk had a substantial advantage in subsequent IQ over those who did not receive mother's milk. (A. Lucas et al., Lancet 1992;339:261-64)

IX

If Christopher Columbus returned today, and looked at the social and environmental damage which the "age of discovery" has lead to, he might well decide that he should have stayed at home. (D. Dickson., New Scientist 1992;1808:2)

X

Chop sticks work for the Chinese because all the work is done by the cook.

XI

A friend in need is a friend indeed.

XII

Laughing is the best medicine.

Theorems belong to the thesis of Ruowei Li entitled 'Functional consequences of iron deficiency in Chinese female workers'.

Wageningen, the Netherlands, 7 May 1993.

To my motherland: People's Republic of China

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Preface

This thesis is the result of four years of research and intense effort. Its successful completion is not only a scientific accomplishment, but also an achievement in international cooperation between Chinese, Dutch, Danish and Swiss scientists and institutions, and as such it can be viewed as an illustration of a Chinese proverb saying that "More logs make a bigger fire". Among the many people who have contributed to this project, I am particularly indebted to the following ones:

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My special thanks will be given to some of my close friends, to the staff members in ICFSN course, to my colleagues (Marie-Louise, Saskia, Eric, and Djoko) in the 'international' office and to the students living with me in Asserpark 44-9A, who took care of me, shared my bitterness and happiness, and made my life sociable and enjoyable during my staying in the Netherlands. The friendship which began in Wageningen will stay forever in my heart.

At last, but certainly not the least, to my parents for all the inspiration and support; to my dear husband for all the love, and painfully waiting for me for such a long time.

Abstract

Women of the reproductive age in China play a very important role in the labour force. Information on anaemia prevalence in this group is hardly available, notwithstanding the fact that iron deficiency anaemia is considered to be a major public health problem in China. Iron deficiency may cause adverse effects on physical performance. However, data available are fragmentary, inconsistent and the results are inconclusive. Furthermore, only a few studies so far have been carried out under free living conditions. The present study was done to resolve some of the uncertainties in this area.

The general objectives of the present study were: 1) to investigate the prevalence of anaemia, its type and the contributing factors to iron deficiency in Chinese female workers; 2) to quantify the functional consequences of iron deficiency in both field and laboratory studies, with emphasis on mean heart rate at work, total energy expenditure at work, and production efficiency defined as the ratio of productivity to energy expended; 3) to identify the effect of iron deficiency per se on physical performance.

In order to study these objectives, both a cross-sectional and an intervention study were designed. The analyses revealed the following results:

--- Prevalence of iron deficiency anaemia was high in Chinese female menstruating cotton mill workers (34%).

--- Oral iron supplementation was effective in the women with poor iron nutritional status.

--- Physical performance, both on the job and in the laboratory tests, was improved with the improvement of iron status. The total energy expenditure at work was reduced and production efficiency significantly increased by 18% after iron supplementation.

--- Marginal iron deficiency may not limit maximal physical work capacity of exercise, but it may cause impairment of prolonged submaximal physical performance.

CHAPTER 1

General Introduction

China, officially called People's Republic of China, is the third largest country in the world, covering an area of 9.6 million square kilometres. The country has a large number of ethnic and linguistic groups. The Han form the largest homogeneous group (about 93 percent) among the 1.1 billion Chinese. Life expectancy for males is 68 years, for females 70 years. Crude birth rate in 1990 was about 21 per 1000 and crude death rate about 7 per 1000 (The State Statistical Bureau of the People's republic of China 1991).

Dietary changes in China

Over the past two decades, particularly since the open policy was adopted and economic reform initiated in 1978, China has made remarkable progress in boosting national economic development and agricultural production. Dietary energy supply increased from less than 1800 kcal (7.53 MJ) per capita per day in 1961-63 to 2560 kcal (10.71 MJ) in 1983-1985 (World Health Organization 1990). Taking the result of the national nutrition survey in 1982 (Institute of Nutrition and Food Hygiene 1985) into account, one can be reasonably sure that, on average, food security in China has already been achieved since the beginning of 1980's. There were corresponding increases in birth weights and childhood growth rates, and infant mortality fell from 200 (per 1000 live births) before 1949 to about 40 in 1980, and to 35 in 1982 (World Health Organization 1990). Improvements in sanitation, health care, diet and the control of communicable diseases account for this reduction in mortality. There have also been significant advances in the control of protein-energy malnutrition.

In all countries, dietary pattern changes with socioeconomic development. In ancient China, as a result of the great disparity in socioeconomic situation between the feudal nobles and the common people, a basic dietary pattern of high-cereal, high - vegetable intake had developed for the common people, while at the same time, a different cereal-based dietary pattern, high in meat and fish, existed for the rich. About 2000 years ago, Confucius taught his students: "The higher the quality of foods the better, and never rely upon the delicacy of cooking". Consequently, the concept of enjoying a diet high in animal food, and a preference for meat and greasy foods, have been shaped over hundreds of years. In the earliest medical classics, a dietary guideline based on experience was given as "Cereals-the basic, fruits-the subsidiary, meat-the beneficial, vegetables-the supplementary". Economic reform and the new policy for agriculture over the past 10 year resulted in a rapid increase in the consumption of foods of animal origin from 26.5 kg/year per capita in 1957 to 47.7 kg/year in 1984 (World Health Organization 1990). Oil intake has also increased as a result of excellent harvests of oil-seed crops. Thus, the national dietary pattern is moving towards larger quantities of animal food, higher fat intake, and smaller quantities of cereals. The obvious increase in consumption of animal foods associated with constant or decreasing consumption of grain indicates an improvement in quality and an increase in the price of the diet.

Current food and nutrition problems

Present nutritional problems in China are characterized by the fact that nutritional deficiencies are still relatively predominant while problems of over-nutrition begin to emerge in some population groups. Adopting the terms used by Campell and his group (Campell et al 1991), it can be said that the disease of poverty and the disease of affluence are presently co-existing in China.

In the rural areas where nearly 80 percent of the Chinese people are living, the food and nutritional problems are primarily those related to inadequacy rooted in under-development and lack of income. Compared with the international standard (World Health Organization 1983), the growth of Chinese children is still below the likely growth potential. Yet of the same concern is the apparent discrepancy between rural and urban

children's growth. From a growth survey in nine provinces in 1987 (Ge et al 1991), the average prevalence of stunting (height for age below the 3rd percentile of the WHO reference) among preschool children aged 0-6 years was 17 percent in urban and 40 percent in rural areas. Average prevalence of wasting (weight for height below the 3rd percentile of the WHO reference) was 4.13 in both rural and urban preschoolers. Apart from protein-energy malnutrition, other specific nutritional deficiencies still exist or even prevail in certain population groups, or certain poor rural and remote sites. It was estimated (Ministry of Public Health 1990) that the current prevalence of rickets in children under 3 years of age was 30-50%; the prevalence of iron deficiency anaemia among under-fives was 30%. There were 7.5 million people suffering from endemic goitre and 38 millions were at risk of iodine deficiency.

Iron status of women in China

Iron deficiency anaemia is the most important nutritional deficiency in China and is usually attributed to inadequate iron intake and/or absorption, high iron demands or blood loss.

Even though Chinese diets, based primarily on cereals and legumes, may contain much iron, without coexisting promoters, they may actually provide only a low level of available iron (FAO/WHO 1988). The availability of dietary iron for absorption is affected by both the form of iron and the nature of the foods concurrently ingested. Two major forms of iron exist in diets: haem iron and non-haem iron. The former, found only in animal sources, is readily available and absorption is not influenced by other constituents of the diet. Absorption of the latter is poor and strongly affected by factors present in foods ingested at the same time. Two widely recognized promoters of iron absorption are animal foods and ascorbic acid (Derman et al. 1977, Sayer & Lynch 1974, Björn-Rasmussen & Hallberg 1974). Many compounds are known to inhibit the absorption of iron, such as phytates (contained e.g. in cereals), vegetable fibres, tannins (contained e.g. in tea), and soy protein (Forth & Rummel 1973, Sharpe et al. 1950). A typical Chinese meal is mainly composed of rice or wheat, vegetables and spices with the addition of some meat. Tea is drunk very often just before or after the meal. Non-haem

iron and large quantities of one or more inhibitors of iron absorption contained in this pattern of diet is partly responsible for dietary quality.

Due to physiological reasons, nutritional iron deficiency is especially prevalent in women of reproductive age, particularly during pregnancy. Although the direct link between reduced iron stores in pregnant women and childhood anaemia has not been definitely established except in severe cases of iron deficiency in the mother (WHO/UNICEF/NUT 1992, Colomer et al. 1990), with the high prevalence of anaemia among children in China, one might assume that anaemia among fertile women would also be a problem. A study on pregnant women in Beijing reported a rapid improvement of iron status after iron supplementation (Wang et al. 1984). Another study showed that 24 to 50 per cent of pregnant and lactating women in Beijing suffered from anaemia (Chinese Academy of Preventive Medicine 1987).

Iron deficiency and physical work capacity

Iron is necessary for the formation of haemoglobin (Hb) in red blood cells and myoglobin in muscles and is important in the function of many metabolic enzymes. The total amount of iron in the body is about 3.5 grams, and 70 percent of this is contained in Hb. The second largest iron compartment in the body is the storage iron in the liver, spleen, and bone marrow. However in women and children, the reserve of iron stores is proportionately much smaller. Other iron compounds are located primarily in solid tissues, e.g., myoglobin and in a large number of oxidative enzymes including the mitochondrial cytochromes and flavoproteins. Iron deficiency is often classified into three stages (Bothwell et al. 1979, Cook & Finch 1979): 1) iron deficiency, characterized by the absence of iron stores; 2) iron deficient erythropoiesis, when an insufficient supply of iron to the erythron can be demonstrated (eg, low transferrin saturation, increased erythrocyte protoporphyrin, or a decrease in the mean corpuscular volume(MCV) by different laboratory methods; and 3) iron-deficiency anaemia, when an insufficient supply of iron to the erythron has reduced the haemoglobin concentration below normal values. Conceptually, iron deficiency anaemia is a type of iron deficiency, but the boundary line between them is rather arbitrary. Haemoglobin concentration, by which anaemia is

diagnosed, is a relatively insensitive index of milder degrees of iron depletion, by the time one becomes anaemic, she/or he is already suffering from a marked degree of iron deficiency.

Hb binds oxygen as blood circulates through the lungs and then releases oxygen to the tissues as blood traverses the capillary bed. Myoglobin is involved in the transport of oxygen across the muscle cells and its storage in muscle. The cytochromes, flavoproteins, and other mitochondrial iron compounds play an essential role in the oxidative production of cellular energy as ATP. Thus, iron plays a major role in oxygen transport and oxygen utilization, both of which are important for the performance of physical activity, since muscular exercise and work involve large expenditures of energy and markedly increase oxygen consumption over resting levels. In iron deficiency anaemia, the delivery of oxygen and uptake by the muscle and the aerobic oxidation of substrate are impaired and anaerobic contraction ensues with consequent build-up of lactate and rapid depletion of substrate, resulting in premature fatigue. It is therefore not surprising that iron deficiency may result in impaired work performance.

The relationship between anaemia and physical work capacity measured by the Harvard Step Test (Brouha et al. 1943) has been established in agricultural labourers in Guatemala (Cifuentes & Viteri 1972, Viteri 1976) and in Indonesia (Basta et al. 1979). A study in anaemic women (Tumbi & Dodd 1990) also showed that the performance on the Harvard step test was improved significantly after iron supplementation.

Since the Harvard Step Test is a relatively crude indicator of physical work capacity and it is difficult to standardize, the measurement of an individual's maximal oxygen uptake ($\dot{V}O_{2max}$) on a cycle ergometer or treadmill is emphasized. $\dot{V}O_{2max}$ is established if there is no further increase in the oxygen uptake with increasing rate of exercise. Studies have indicated that workers involved in more or less heavy manual labour, and who can set their own rate of work spontaneously, exercise up to a level of 40 per cent of their maximal aerobic power during an 8-hour work day (Åstrand & Rodahl 1988). Therefore, maximal aerobic capacity, which is equivalent to the highest oxygen uptake ($\dot{V}O_{2max}$), plays a decisive role on one's work capacity. Within certain limits the level of haemoglobin is correlated with $\dot{V}O_{2max}$ (Kjellberg et al. 1949; Sproule et al. 1960, Vellar & Hermansen 1971, Ekblom et al. 1972, Davies et al. 1973, Woodson

1984, Scrimshaw 1984). Blood transfusions to correct anaemia result in an almost immediate improvement in work performance (Edgerton et al. 1981).

While studies of maximal physical performance during exercise have defined some of the limits imposed by iron deficiency anaemia, it is difficult to translate such findings into the every day living condition in countries where iron deficiency is rife. Manual labourers are rarely required to perform tasks that require maximal physical effort, and even when they do the circumstances are different from those normally applied in physiological laboratory testing. They do not continue their tasks until exhaustion is reached, but rather carry them out intermittently, with periods of hard labour followed by recovery periods. It is clear that other approaches are required if meaningful information is to be obtained on the overall working capacity of an iron-deficient population. An alternative approach to the problem has been applied to field studies directed to find out whether the productivity of the workers is related to their iron status, as well as the voluntary activity level one chooses. The relationship between the Hb concentration and physical performance was further defined in studies on agricultural labourers in Guatemala (Viteri & Torun 1974), Sri Lanka (Edgerton et al. 1979,1981,1982; Gardner et al. 1977) and in Indonesia (Husaini et al. 1983, Basta et al. 1979). Edgerton et al found that the amount of tea picked increased significantly from 16.2 to 16.4 kg/day, while Hb increased from 10.8 g/dl to 12.7 g/dl after one month of iron treatment. The largest effect was demonstrated in those subjects with the most severe anaemia. Perhaps the most subtle behavioural effect of any deficiency might be the amount of physical activity that one 'feels' like doing voluntarily. The attempt to quantify this 'feeling' is extremely difficult. In the same fore-mentioned study , Edgerton and his coworkers recorded levels of activities using a movement-sensing device secured to the ankle with a watch band attached to an oscillating spring device. About 19 days after the iron treatment, the amount of activity was significantly greater and the Hb rose from 8 to 11 g/dl, while the improvement of productivity (kg tea picked per day) was not evident during this period. The results from field studies are probably more relevant to one's daily life than exercise performance on a treadmill or cycle ergometer. The effects of iron deficiency anaemia on work productivity have profound economic implications. The treatment of iron deficiency may influence not only the occupational work performance, but also his/her other physical activities and/or life pattern as well as those of other family members. The positive cost-benefit effects of iron treatment and the net

productivity effect could be apparent.

Motivation and the aims of the present study

The economy of China still heavily depend on manual work. The labour force in 1982 was more than 47 percent of the total population (Encyclopædia Britannica, Inc. 1988). Women play a considerable role in the economic development of the state. The number of female workers and staff in the non-agricultural sectors increased from 600,000 in 1949 to 48.69 million in 1987, representing 36.8 per cent of the total labour force in 1987. Their fields of employment have extended far beyond the traditional spheres. The output value of women's production in agriculture and industry in well developed areas accounts for 55-65 per cent of the total commodity output value.

With the high prevalence of anaemia among children and pregnant women in China, one might assume that anaemia among female menstruating workers would also be a problem. The improvement of iron nutritional status in female workers presumably leads to the increase of the productivity, furthermore there are other important health benefits that cannot be expressed in financial terms. Unfortunately, as with nutrition in general, information about anaemia prevalence in female labours is hardly available.

The muscular work in daily life is very seldom maintained for very long at a steady rate and until exhaustion is reached. For these reasons, the laboratory tests with a treadmill or cycle ergometer in many ways represent an artificial situation. It seemed desirable to determine whether there might be more subtle and practical effects of iron deficiency anaemia. There are indications in the literature that the productivity of anaemic workers is reduced. A major problem with the studies, which focus on the relationship between iron deficiency and work performance, is that productivity can be complicated by social, economic, and motivational factors. In other words, when highly motivated, the anaemic people may achieve the same productivity as the normal ones by spending more energy. Elevated energy expenditure during work may make workers accomplish their tasks with undue fatigue, so that at the end of the working day, they are left with insufficient vigour to enjoy their leisure time and performing their social duties.

Since the ultimate goal of any nutritional intervention programme is to improve the overall well-being of the target population, both at work and during leisure time, the total energy expenditure at work and the magnitude of the impact of iron deficiency on work performance need to be investigated.

It is clear that anaemia itself has a marked effect on physical performance. It is also suggested that there may be some non-Hb-related iron deficiency effects (Rowland & Kelleher 1989, Finch et al. 1976, Weaver & Rajaram 1992). In one study with two groups who had similar Hb levels but different serum iron levels, the group with the higher serum iron was able to exercise longer on a treadmill (Ohira et al. 1981). In another study, the heart rate was found to be reduced at a given work load and work time elevated following iron treatment more than would be expected at a given Hb level (Edgerton & Ohira 1982, Ohira et al. 1979). Improved work output was also observed in field studies in rubber latex tappers in Indonesia (Basta et al. 1979) after correction of iron deficiency, prior to any changes in Hb status. These results provide evidence that there are effects of iron on work performance that can not be attributed to Hb. However, the data are not consistent and the results are still inconclusive.

These were the reasons why this study was undertaken with the following general objectives: 1) to investigate the prevalence of anaemia, its type and the contributing factors to iron deficiency in Chinese female workers; 2) to quantify the functional consequences of iron deficiency in both field and laboratory studies, with emphasis on heart rate, energy expenditure, and production efficiency defined as the ratio of productivity to energy expended; 3) to identify the effect of iron deficiency per se on physical performance.

This research on the functional consequences of iron deficiency will hopefully strengthen the action for iron deficiency prevention, in order to reach the goals set by several international agencies for the substantial worldwide reduction of iron deficiency anaemia by the year 2000.

The outlines of the study

The present research was designed as follows:

1. The first phase consisted of a cross-sectional study in Chinese female cotton mill workers, in order to assess the prevalence of anaemia and factors contributing to it.

2. In the second phase, an intervention study was designed in this population in order to assess the functional consequences of iron deficiency using parameters, such as mean heart rate at work and during leisure time; energy expenditure at work and during leisure time; physical activity pattern; production efficiency; heart rate and respiration rate during exercise; cycling efficiency and maximal oxygen uptake ($\dot{V}O_{2max}$).

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CHAPTER 2

Prevalence and Type of Anaemia in Female Cotton Mill Workers in Beijing, China

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ABSTRACT

This study investigates the prevalence and type of anaemia in Chinese female cotton mill workers. The prevalence of anaemia is reported of 447 non-pregnant female workers aged between 19 to 45 years. The mean value of haemoglobin (Hb) was 123 (SD 15) g/l and 150 out of the total 447 subjects had Hb values below 120 g/l, thus 34% of the population was anaemic according to WHO criteria. The mean value of free erythrocyte protoporphyrin (FEP) was 419 (SD 215) ug/l, 55% of the total population had FEP values higher than 350 ug/l and 72% among the anaemic subjects. Serum ferritin (SF) was tested in all the women with a Hb value less than 120 g/l and 71% of them had SF values below 12.0 ug/l. 80 women diagnosed as either iron deficient or iron deficiency anaemic were selected for a diagnostic supplementation trial. They were randomly assigned to ferrous sulphate (60 or 120 mg of iron/d) or placebo treatment for 12 weeks. Iron supplementation increased mean Hb values from 114 to 127 g/l

($p<0.001$) and SF levels from 9.7 to 30.0 ug/l ($p<0.001$), and decreased mean FEP values from 570 to 277 ug/l ($p<0.001$). The response rate of Hb in the whole iron treated group or iron treated subjects with a Hb less than 120 g/l was 90% or 92% respectively. These findings indicate that the type of anaemia in this population was mainly iron deficiency. It was also found that in this population the severity of anaemia, not the prevalence, was significantly related to the use of intra-uterine devices (IUDs).

INTRODUCTION

China has the largest female work force in the world. Women, who constitute about 40 per cent of the total labour force, have played a considerable role in developing the country and their fields of employment have extended far beyond the traditional spheres (United Nations Children's Fund, 1989). The nutritional status of female labourers is presumably closely related to their working and living conditions, but unfortunately, information on their nutritional status is very limited.

According to the second national Chinese dietary survey in 1982 (Institute of Nutrition and Food Hygiene, 1985), the average food consumption of adults in both rural and urban areas was found to be adequate except for calcium and riboflavin. Specific data by region of the country or for women of child-bearing age are however not available. Indirect per capita nutrient availability calculation in 1985 produced results similar to the 1982 survey, except that the mean intake of protein was estimated at about 82 per cent of the Chinese Recommended Daily Allowance established by the Chinese Nutrition Society in 1988 (Jian, 1990). The nation-wide nutrition survey in 1982 also showed that 92% of dietary energy came from plants and only 8% from animals. The main source of energy was from cereals, accounting for 71%, which was even higher among people living in rural areas. Therefore the bio-availability of much of the iron in the average Chinese diet may be restricted. In addition to the problem of limited iron absorption, excessive menstrual blood losses is one of the likely causes of iron deficiency among Chinese women. It was reported that modern contraceptive practices can

significantly modify menstrual blood loss. For example, the mean menstrual blood loss is reduced by half in subjects taking oral contraceptive, but is doubly increased in subjects using intra-uterine devices (IUDs) (International Nutritional Anaemia Consultative Group, 1984). The latter practice is more common among Chinese women, because of the safety, efficacy, economy and ease of using intra-uterine devices. There were approximately 84 million women using an IUD in 1987 all over the world, of whom about 60 million were in China (World Health Organization, 1992a).

The present study, conducted from 1989 to 1991 in Beijing, was designed to investigate the prevalence of anaemia, its type and the contributing factors for iron deficiency in Chinese female menstruating cotton mill workers.

SUBJECTS AND METHODS

General information

The study was carried out in one of the three largest textile factories in China. These three cotton mills are located in the eastern suburb of Beijing and all have a similar structure. In each factory, about 8000 employees are manual workers, of whom more than 80% are females. The major work in the factory is carried out in the yarn spinning workshop, where almost all the workers are females. Both the quantity and quality of their work reflect the general workload of female textile labourers. Therefore the female employees in the yarn spinning workshop were selected as the study population. The activities in this workshop are generally very monotonous; the women mainly work with their arms and hands while standing and walking along the machines. Since the machines never stop, the workers work in a running shift with two days' morning shifts (6.30 to 14.30 hours), two days' afternoon shifts (14.30 to 22.30 hours), two days' night shifts (22.30 to 6.30 hours) and two days off for each worker.

Screening Test

All the non-pregnant female labourers aged between 19 to 45 years working in the yarn spinning workshop were invited to come to the factory clinic for examination. The response rate was 95%. 30 out of 558 female workers did not show up simply either because they could not leave the job at that time or because they were afraid of blood sample collection. Due to technical problems, haemoglobin (Hb) and free erythrocyte protoporphyrin (FEP) could only be determined in 447 subjects. Serum ferritin (SF) was tested in all the subjects with Hb values less than 120 g/l (n=150) and, in addition, in 118 subjects with Hb values more than 120 g/l, therefore SF was tested totally in 268 subjects.

Diagnostic Supplementation Trial

Since the diagnosis of iron deficiency (ID) and iron deficiency anaemia (IDA) based upon the cut-off values for Hb, FEP and SF is rather arbitrary, the response to iron supplementation was also studied to investigate the type of anaemia in this population. From the screening tests on Hb and FEP (n=447) and SF (n=268), 147 subjects were diagnosed either as iron deficient or as having iron deficiency anaemia based upon the following criteria (Cook, 1982; DeMaeyer, 1989): Iron deficiency anaemia (IDA) was regarded as being present when the haemoglobin concentration was below 120 g/l and either SF < 12.0 ug/l or FEP >350 ug/l. When Hb level was normal, but both the values of SF < 12.0 ug/l and FEP > 350 ug/l, iron status was categorized as iron deficient. Out of the 147 subjects, 83 women were selected for a diagnostic supplementation trial after a routine medical check-up. They were randomly divided into two groups and treated for 12 weeks with either iron or placebo. Three subjects dropped out of the study. One subject was not willing to participate in the intervention trial. One became pregnant and one resigned from the job. Finally the data of 80 subjects were used in statistical analysis. Both before and after treatment, body weight, body height and fat free mass (FFM) were measured and capillary blood was collected in the morning,

in the fasting state, after emptying the bladder, and after an overnight stay in the factory hospital.

Ferrous sulphate pills containing 60 mg iron and placebos were provided by Lomapharm Medicine, Emmerthal, Germany. The supplementation trial was done over the whole year. But in each season, the placebo and iron-treated subjects received pills simultaneously. Both medicine distributor and the subjects were blinded. Pills were distributed every day to each subject under supervision. In other words, the subjects had to take the pills in front of the distributor. ID and mild IDA (above 80% of the cut-off Hb value) subjects were given one pill per day of either iron (n=34) or placebo (n=36), moderate (between 60 and 80% of the cut-off Hb value) subjects were given two pills per day of either iron (n=6) or placebo (n=4). In the intervention trial, no subjects were severe IDA. During the days off (two of eight days), the subjects took the pills at home. In case they would forget to take the pills at home, they were instructed to bring them back.

Dietary and Socio-demographic Survey

In order to investigate the contributing factors for iron deficiency, information on food intake, health history and socio-demographic information were obtained by structural interview from the 80 ID and IDA cases and in addition from 80 controls who were also involved in the screening test having a Hb at or above 120 g/l and either SF $\geq$ 12.0 ug/l or FEP $\leq$ 350 ug/l. The controls were matched with the cases for age, sex and type of work.

The dietary history method (Haraldsdottir, 1988) was used to assess the subjects' food intake over the past month. A questionnaire according to the characters of the Chinese diet was carefully prepared. The information was obtained by a fixed person with relevant training in the food and nutrition fields. The individual interview lasted about 1 to 1.5 hours. It started with a 24 hours recall, then each meal was discussed in turn to find out which food were used and how often, what alternatives might be used on other days of the week and any irregularities in the eating pattern, so that a menu was

established for the whole month. Usual portion sizes were estimated with the aid of different types of food containers and given information was cross-checked using a list of individual foods as a memory aid.

Haematological measurements

Capillary blood was obtained by left ring finger stick using disposable blood lancets (Lameris, The Netherlands). The first drop of blood was discarded and spontaneous flow of blood was provided. Haemoglobin (Hb) was determined in duplicate by HemoCue method (Laifer et al. 1990).

Serum ferritin (SF) was determined in duplicate with a commercially available Enzyme Immuno Assay (ELISA) kit (Ramco, Laboratories,INC., USA) (Li et al. 1978) using Titertek Multiskan R plus (EFLAB, Labsystems and Flow laboratories, Finland).

Free erythrocyte protoporphyrin (FEP) was determined by fluorescent spectrophotometry (DaoJin, 12F-510, Japan), using the method of Piomelli (1976) with some modification (Chen, 1981). The reproducibility of the determination was found to be 4% and the day to day variation was found to be from 4 to 8%.

Anthropometry

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm respectively using a beam weighing scale and measuring system (Seca Model 220, Germany). The weight of the patient's cloth was measured separately and subtracted from the total weight.

Bioelectrical impedance analyses (RJL Systems, USA) were performed in duplicate after voiding, at the right side of the body as described by Lukaski et al. (1986) and Deurenberg et al. (1988). Empirically derived formulas provided by the manufacturer

of the instrument were used to calculate estimated FFM.

Statistical analysis

All statistical analyses were done using the SPSS/PC$^+$ programme (1988). The results of Hb, SF and FEP after intervention were compared with the pretreatment results by two-tailed paired Student's t test. The straight-line regression of the change of Hb value on initial Hb value was specified with regard to different treatment, using multiple regression SPSS/PC-programme with treatment as dummy variable (placebo group = 0, iron-treated group = 1). Parallelity of the two lines was tested by the interaction effect as described by Kleinbaum and Kupper (1978). Comparisons between cases and controls were done using two-tailed two sample Student's t test and chi-square test where appropriate. The dietary history survey was analyzed by the Chinaprj software designed by the Chinese Academy of Preventive Medicine, Beijing, 1987, which is based on the Chinese Food Composition Table published in 1982.

RESULTS

Table 1 describes some haematological, anthropometric and demographic variables in the total study population, in cases and in controls. The mean value of Hb among 447 subjects was 123 (SD 15) g/l. 150 out of 447 Hb values were below 120 g/l, accounting for 34% of the total population; of them, 78% were in the range between 100 to 120 g/l, 20% between 70 to 100 g/l and 2% below 70 g/l. The mean FEP value was 419 (SD 215) ug/l. 55% of the FEP values were higher than 350 ug/l in the total population but 72% in the anaemic subjects with Hb below 120 g/l. SF was mainly examined in women with Hb below 120 g/l. The mean SF value in the total sample was 23.2 (SD 28.2) ug/l, but the mean values of SF among the subjects with Hb at or above 120 g/l and among the subjects with Hb below 120 g/l were 38.7 (SD 35.3) ug/l and 11.1

(SD 10.7) ug/l respectively. 71% of the anaemic subjects had the SF values below 12.0 ug/l and 83% below 15.0 ug/l.

Table 1. Profile of the Biochemical, Anthropometric and Demographic Values

Variables	Total Population		Cases(N=80)		Controls(N=80)		
	Mean	SD (n)	Mean	SD	Mean	SD	
Age(y)	29.2	7.9(447)	29.9	6.0	30.6	5.5	
Working Duration(y)	7.7	6.6(447)	10.6	6.5	11.1	5.6	
Hb(g/l)	123	15(447)	115	14	130	7	*
FEP(ug/l)	419	215(447)	535	246	389	157	*
SF(ug/l)†	23.2	28.2(268)	10.0	8.7	42.7	28.9	*
Height(cm)		-	160.8	5.1	159.9	4.7	
Weight(kg)		-	54.6	6.9	56.7	6.7	
Fat free mass(kg)		-	39.8	4.0	38.3	3.4	
Education level(y)		-	9.5	1.3	10.1	1.2	*
Family income(Yuan/month)‡		-	404.4	70.8	465.3	43.9	*
Menstruation Duration(d)		-	6.6	2.9	6.0	2.4	
Duration of using intra-uterine devices(y)		-	3.4	3.1	4.6	4.1	

Hb, haemoglobin(g/l); SF, serum ferritin(ug/l); FEP, free erythrocyte protoporphyrin(ug/l).

Mean values for iron deficient cases were significantly different from controls: * $p<0.01$.

† SF was tested only in all the subjects with Hb value less than 120 g/l (n=150) and in 118 subjects with Hb value higher than 120 g/l.

‡ One US dollar was equivalent to 5.4 Chinese yuan.

The findings of the double blind intervention trial are given in **Figure 1** and **Table 2.** Figure 1 shows that one person in iron-treated subjects with a Hb < 120 g/l fell below the regression line of the change of Hb levels on the initial Hb levels for placebo group. Since the non-responders in the iron-treated group must be assumed to be symmetrically distributed around the placebo regression line, the total numbers of non-responders in the iron-treated subjects with a Hb < 120 g/l may be 1 x 2 =2 subjects (Garby et al. 1969). Consequently a high response rate in iron-treated subjects with a Hb < 120 g/l was obtained, i.e. 22/24=92%. Similarly the response rate of 90% is calculated among the whole iron treated group. The regression analysis showed that the relationship between the change in Hb level and the initial Hb level was significantly different between the iron-treated group and the placebo group (p=0.013), the improvement was much more pronounced in iron-treated group.

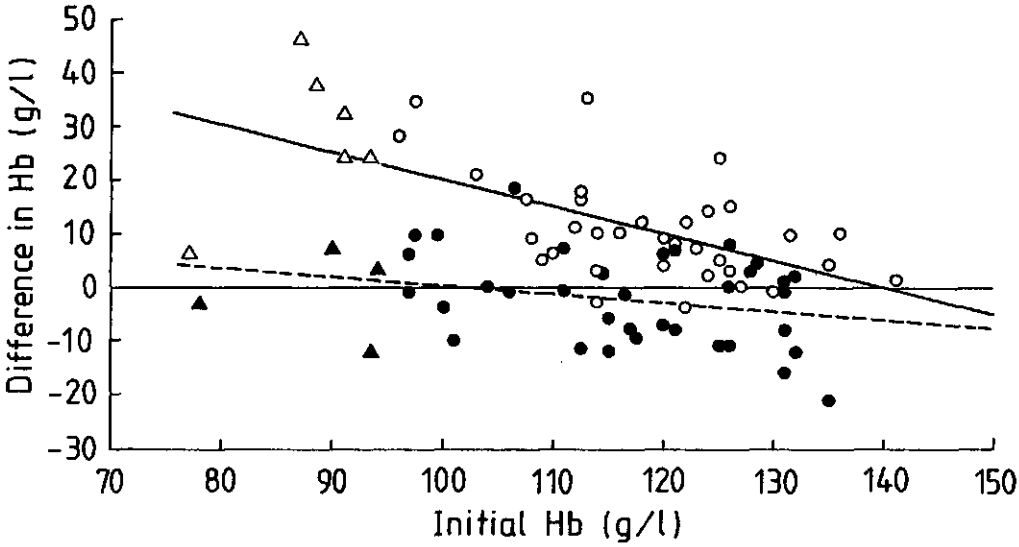

Figure 1. The relationship between response in haemoglobin (Hb) and initial Hb levels (o—▵ : iron-treated subjects receiving one or two pills per day respectively. ●---▲ : placebos receiving one or two pills per day respectively).

Table 2. Evaluation of haematological status of the subjects before and after 12 week treatment with either iron or placebo

Parameters	iron (N=40)		placebo (N=40)		
	Mean	SD	Mean	SD	
Haemoglobin(g/l)					
before treatment	114	15	115	14	
after treatment	127	12	113	14	
difference(95%CI)	13	12(9,17)**	-2	8(-5,1)	††
Serum ferritin (ug/l)					
before treatment	9.7	5.6	10.6	10.9	
after treatment	30.0	20.8	18.8	17.9	
difference(95%CI)	20.3	18.9(14.3,26.3)**	8.2	19.4(2.1,14.3)*	†
Free erythrocyte protoporphyrin(ug/l)					
before treatment	570	308	525	168	
after treatment	277	113	372	150	
difference(95%CI)	-296	264(-379,-213)**	-153	144(-199,-107)**	†

95 % CI, 95% confidence interval.

The values after treatment were significantly different from pretreatment results by paired t test: * $p < 0.05$ and ** $p < 0.001$.

The values are significantly different between two groups by group t test: † $p < 0.01$ and †† $p < 0.001$.

Differences in some socio-demographic variables between cases and controls are shown in **Table 1.** The results indicate that the level of education and average family income were significantly lower in cases. In the present study population, 46 out of 64 women in iron deficient cases and 48 out of 58 in normal controls practising contraception were using IUDs. The analysis did not show that IUD practising was a contributing factor for iron deficiency compared with other contraceptive practices such as pills and condom ($X^2=1.87$, $df=1$, $p>0.05$). However a significant difference in the severity of iron deficiency was found between subjects using IUDs for more than two years and for less than two years. In ID subjects having IUDs, only 9 out of 22 used them less than two years; but in mild and moderate IDA subjects having IUDs, 17 out of 24 used them less than two years ($X^2=4.18$, $df=1$, $p<0.05$). Women wearing IUDs for less than two years showed more severe iron deficiency.

Table 3 shows the daily nutrient intake and sources of energy between cases and controls.

DISCUSSION

Prevalence of anaemia

A mean Hb value of 123 g/l and a mean FEP value of 419 ug/l were found in the examined 447 female menstruating cotton mill workers. The World Health Organization (WHO) has proposed Hb value of 120 g/l as the lower limit of the normal range for adult non-pregnant females (World Health Organization, 1968b).In this study sample of 447 female cotton mill workers, 34% of all the subjects had Hb values below the limit of 120 g/l. This result is similar to that of the region reports from the second national dietary survey in 1982 and much higher than the anaemic prevalence among

adult males, which was found to be 14% on average (Institute of Nutrition and Food Hygiene, 1985).

Table 3. The Comparison of Daily Nutrients Intake and Sources of Energy between Cases and Controls

Parameters	Cases (N=80)			Controls (N=80)			
	Mean	SD	RDA%+	Mean	SD	RDA%	
Energy(KJ)	8995	2755	80	8903	2345	79	
Protein							
g	75	29	94	75	26	94	
energy%	14	5	-	14	3	-	
animal source%	34	12	-	33	13	-	
Fat							
g	87	35	-	84	35	-	
energy%	36	9	-	35	9	-	
Carbohydrate							
g	269	89	-	270	77	-	
energy%	50	10	-	51	9	-	
Iron(mg)	17	6	94	22	5	122	*
Vitamin A (ug retinol equivalents)	797	278	100	1137	466	142	*
Thiamin(mg)	1.1	0.6	79	1.1	0.4	79	
Riboflavin(mg)	0.9	0.4	64	0.9	0.4	64	
Ascorbic acid(mg)	111	59	185	136	52	277	*

Mean values for iron deficient cases were significantly different from controls: * $p<0.01$.

+ Recommended daily allowance established by Chinese Nutrition Society.

Although specific data for female workers are not available in China, the prevalence of anaemia in this study population is among the range of that in fertile women (21 to 55%) reported by the regional health organization (Institute of Nutrition and Food Hygiene, 1985). Furthermore the average age, height and weight in the present study sample were comparable to those studied in female workers (29 years, 160 cm, 56 kg against 27 years, 158 cm, 53 kg respectively)(Yu, 1982). On the other hand, the energy expenditure at work measured in this study (unpublished data) is similar to the data obtained from other population of female cotton mill workers by the Health Institute, Chinese Academy of Preventive Medicine (9.7 KJ/min against 11.0 KJ/min)(Yu, 1982). Therefore, one might assume that this study population could at least represent Chinese female cotton mill workers, who play a very important role in state economy.

The type of anaemia

Initially 12.0 ug/l of SF value was proposed as the lower cut-off value for iron deficiency. More recent studies propose a SF value of 15.0 ug/l to be indicative of iron deficiency (Hallberg & Rossander-Hultén, 1991). By these definitions, respectively, 71% or 83% of the anaemic subjects in this population were iron deficiency type. Based upon 350 ug/l of FEP as a cut-off value for iron deficiency, 72% of the anaemic subjects were regarded as iron deficiency. Therefore it was assumed that iron deficiency was the major type of anaemia in this population. However it is known that the cut-off values of haematological parameters for diagnosing ID and IDA are arbitrary and may not be appropriate for all given geographic areas and population, therefore the iron supplementation trial constitutes an important step toward defining the nature and extent of nutritional deficiency (World Health Organization 1975c). The evidence that the anaemia in this population was of the iron deficiency type was actually derived from the high response to iron supplementation in the iron treated subjects with a Hb less than 120 g/l.

The diagnosing boundary line between iron deficiency and iron deficiency anaemia could be both indefinite and shifting, therefore both iron deficiency and iron deficient anaemic subjects were selected for the intervention trial. Since the analysis

results were not significantly influenced when omitting the subjects receiving two tablets per day, the data from the subjects receiving one or two tablets were combined in Table 2. Table 2 shows that the initial values of all the haematological parameters were identical between the iron-treated and the placebo group. The increase in Hb value in the iron-treated subjects was statistically significant, while the Hb value in placebo group remained almost constant. Although the changes in SF and FEP in the group receiving placebo were also significant, the subjects receiving iron treatment showed a significantly greater increase in SF and decrease in FEP. The regression analysis of the change of Hb on the initial Hb level also showed that the rise in the Hb value was significantly attributed to the iron treatment. These indicate that not only iron deficient anaemic subjects but also iron deficient subjects diagnosed on the basis of the haematological cut-off values were indeed lack of iron. Therefore the assumption that iron deficiency was the major type of anaemia in this population based upon the cut-off values may be considered as correct. The reason for the change in SF and FEP in the placebo group could be due to the fact that a programme on nutrition education given in combination with the project may have influenced the subjects to pay more attention to their food intake. In the placebo-treated group, the increase in SF and the fall in FEP levels were significant with no corresponding increase in Hb values. For SF, this could be due to the relatively high variability from day to day. For FEP, this remains unclear. FEP has a relatively high stability. Although seasonal variation could have had an effect, it was under control in this study, as placebo and iron-treated groups were studied simultaneously. In the iron-treated group, at least one haematological parameter was improved to the normal level in all the subjects, but still approximately 10% of the subjects failed to reach the normal limits of all the three haematological parameters after treatment with iron for 12 weeks. The dropout rate was small in this study (3.6%) and appeared unrelated to side effects of iron treatment. There were only four spontaneous complaints concerning side effects and these tended to disappear after a couple of days.

Contributing factors for iron deficiency

The causes of iron deficiency for menstruating women are multiple and can be

due to low iron intake, poor iron absorption, increased iron losses and poor iron utilization.

Based upon the physiological iron losses and bioavailability of dietary iron consumed from general Chinese diet, the Chinese Nutrition Society established 18 mg as recommended daily allowance (RDA) of iron intake for menstruating adult females. In the present study, the calculated iron intake in both iron deficiency cases and in normal controls meets the Chinese RDA (see Table 3). Previous studies had the same findings (Wang et al. 1983). The apparent paradox of a high prevalence of nutritional iron deficiency in women with 'high' iron intake could be due to poor bio-availability of iron in the diet, higher iron requirement in women using IUDs (Hallberg & Rossander-Hultén, 1991) or due to an overestimation of iron contents in the Chinese food composition table used. It has been reported that the iron content of foods analyzed by a colorimetric method, as used in making the Chinese food composition table, was higher than that being analyzed with atomic absorption (Hong et al. 1983). Although the food consumption data in this study were not validated, a comparison of the dietary intake between the different groups using the same method may indicate real differences.

Blood losses have a profound effect on iron balance. The major cause of blood loss in Chinese fertile women may be the menstrual blood loss. In developing countries, IUDs are widely used among married women, which increases menstrual blood loss by between 35% and 146% depending on the type of device (Hefnawi, 1974; Guillebaud et al. 1976). Stainless steel IUDs are the most common type used in China. It has been reported that such devices increase mean menstrual blood loss by 54% within one year after inserting them (Yuan et al. 1987). In the present study, no relation was found between iron deficiency and different contraceptive practices. One major reason could be that IUDs were applied to most of the women practising contraception in our study, which was 83% on average. However, the severeness of iron deficiency was found to be related to the duration of using IUDs. The complaints of our subjects were also in accordance with this finding, i.e. menstrual blood loss was increased by using an IUD especially during the first two years. This implies that the longer the IUD practice lasts, the more the women get adapted to. Therefore it is suggested that iron supplementation should be given to the IUD users suffering from menorrhagia, especially during the first few years.

In summary, a high prevalence of anaemia (34%) was found in Chinese female menstruating cotton mill workers and the major type of anaemia in this population was iron deficiency. Low availability or utilization of iron, and excessive blood loss in IUD users may be the most common factors leading to iron deficiency and iron deficiency anaemia in this population. Although the causes of iron deficiency in this population could not be determined from this study, oral iron treatment was found to be effective and iron supplementation to IUD users suffering from menorrhagia may well be beneficial.

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CHAPTER 3

A Critical Evaluation of Heart Rate Monitoring to Assess Energy Expenditure in Individuals

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ABSTRACT

The prediction of energy expenditure (EE) from minute-by-minute heart rate (HR) recording was evaluated in 40 female workers, with emphasis on the inter- and intra-individual variation of this method. The results show that the relationship between EE and HR varied greatly between and within subjects. The coefficients of inter- and intra-individual variation were 14-18% and 11-20% respectively. The poor limits of agreement in EE (mean difference $\pm$ 2 SD) between group and individual calibration curves indicate that estimated EE from group curves is inferior to estimated EE from individual curves. Therefore it is concluded that, to have the best estimates of individual EE, only individual calibration curves should be used. At different occasions these curves should be generated again. Since the limits of agreement in EE between individual curves based on 18 and 9 different activities were rather wide (-2399 KJ/16h to 1817 KJ/16h), it is preferable to have a wide range of different activities in the individual calibration procedure.

INTRODUCTION

A variety of methods (1-3) have been used to investigate daily energy expenditure (EE). Currently the doubly labelled water method and heart rate (HR) monitoring are two of the most acceptable and objective methods for estimating EE over a long period. The ability of the heart rate method to provide information on within- and between-day variability in activity levels makes it for certain purposes preferable to the doubly-labelled water method, irrespective of the cost difference.

Most previous attempts to predict EE from HR have been based upon accumulated or averaged HR over the entire period of time under investigation (4-6). The mean HR is usually converted to EE from individual regression lines derived by calibrating each subject with a series of submaximal workloads. The main problem with this approach is that usually mean HR over an entire day is quite close to resting HR, which is often not discernibly related to EE. With the development of small and light devices for minute-by-minute HR recording, computer storage of the data and the ability to examine the HR data rapidly by computer, the method has been substantially improved. The general findings are that the minute-by-minute HR recording method can be considered as a relatively inexpensive, yet accurate technique for estimating daily EE of population groups (7-9). In addition to accuracy, the variation of the method between and within subjects needs to be determined before an evaluation of the methodology can be completed. To our knowledge no study on the variation of the minute-by-minute HR recording method between and within subjects has been performed. Therefore, the purpose of this study was to investigate the inter- and intra- individual variation of EE estimated from minute-by-minute HR recording.

SUBJECTS AND METHODS

Subjects

Forty non-pregnant female cotton mill workers in Beijing, aged between 20 and 45 years, were the subjects for this study. They all were engaged in moderate physical activities, had no acute or chronic diseases except for iron deficiency or mild iron deficiency anemia. The measurement of the relationship between EE and HR was done twice in each subjects with an interval of 12 weeks.

Experimental design

The subjects stayed the night before the measurement of basal metabolic rate (BMR) in a comfortable laboratory. BMR and HR were determined in the morning. BMR was tested under standard conditions from two 10-minutes samples of expired air after a 5 minute stabilization period. Body weight and body height were measured (Seca Model 220, Germany) followed by a standard breakfast containing about 2100 KJ. Thirty minutes after breakfast, the calibration procedure involving simultaneous measurements of EE and HR started on the subjects who were asked to carry out a number of activities similar to those encountered in normal daily life. The day before or after the calibration procedures, minute-by-minute heart rates in free-living conditions were recorded for the whole day when the subjects were out of bed. The total energy expenditure over the sampling period was calculated by adding up every minute's EE estimated from the corresponding HR using the individual calibration curves. For a better comparison, the energy expenditures were all adjusted to a period of 16 hours. About 12 weeks later, all fore-mentioned measurements were repeated in an identical way, yielding a second calibration curve for each woman.

The estimation of energy expenditure from minute-by-minute heart rate recording

1. Calibration procedure

The principle of the estimation of EE from minute-by-minute HR recording is that a relationship exists between HR and EE (2,7). In order to determine the HR-EE regression lines, a calibration procedure was done on each subject twice with a interval of about 12 weeks. In addition to two BMR measurements, the whole procedure consisted of measuring 16 different activities: sitting and standing quietly, sitting and standing with hands or arms movement, sweeping the floor, kneebending, cycling at workloads of 0, 30, 40, 60 and 80 Watts (Monark 818E, Sweden), stepping on a single standard stair and on multiple stairs, as well as the normal working activity in the factory. During activities like kneebending, cycling and stepping, a metronome (Taktell, Willner, Germany) was used to standardize the conditions. Between the measurements, the subjects were asked to relax allowing the HR to reach the basal level. Generally, a 10-minutes break was allowed for light activities, and 30-minutes for heavy activities.

EE and HR were determined simultaneously during the last 3 to 5 minutes of each activity after preliminary stabilization. EE was measured by the Douglas bag technique. Oxygen and carbon dioxide contents and the volume of the expired air were determined by a paramagnetic oxygen analyzer (Servormex 570A, England), an infra-red carbon dioxide analyzer (Servomex 1410, England) and a precision wet gas meter (Schlumberger, the Netherlands) respectively. Gas volumes were corrected to standard temperature and pressure (STPD). Each day, the gas analyzers were calibrated by pure nitrogen gas and by a standard gas mix containing 3.5% of CO_2, 17.3% of O_2 and 79.2% of N_2. The flow of the precision gas meter was controlled at a speed of 1750 L/h. Finally energy expenditure was calculated as described by Consolazio et al (10). HR was recorded using a Sport Tester™ PE-3000 (Polar Electro, Kempele, Finland). The calibration point for each activity was computed as the mean of the HR and EE values respectively for the sampling period.

2. Minute-by-minute heart rate recording in free-living conditions

Just the day before or after the calibration curve was completed, minute-by-minute heart rate was recorded in free living conditions for about 16 hours. The HR monitor system consists of an electrode-belt transmitter and wrist microcomputer receiver that stores the pulses in a memory. Pulses are recorded at 1-minute intervals up to a maximum recording time of 18 hours, when stored information was retrieved and the memory reprogrammed. Each subject was fitted with the HR instrumentation early in the morning, it was worn until it was removed by the subject before going to bed in the evening. Information of each minute's HR was retrieved via an interface unit and computer for which an additional program was written to compute EE from HR. A drawback encountered with the HR monitors was that electrode belt occasionally came loose as subjects followed their normal daily activities, resulting in lost transmissions. One subject experienced moderate skin irritations. However, generally the protocol was well accepted by the subjects.

3. Calculation of energy expenditure

Eighteen levels of EE (KJ/min) at different HR (beats/min) were obtained from the calibration procedure. According to the literature (11), the logistic regression fit the data well. The present data were also best fitted by logistic function after a variety of other regression models were attempted (unpublished data), including using two separate straight lines, one straight line and some other curvilinear lines. Therefore, the curvilinear relationship between EE and HR was modelled as a logistic function: $EE = BMR + C*\{1+\exp(A-B*HR)\}^{-1}$, whereas EE and BMR in KJ/min and HR in beats/min. For each subject, the 'best values' of A, B and C were assessed from her EE and HR values observed on different activities using non-linear regression computer program (12). The group means (SD) for A, B, and C were 9.88 (2.10), 0.092 (0.023), and 20.12 (2.63) respectively. The fit of the calibration curves was quite satisfactory, as judged from the higher square multiple correlation coefficient (R^2) (**Figure 1**).

After the individual HR-EE relation was determined, EE of every minute was derived from the HR recording using the individual HR/EE calibration line. Total energy expenditure over the entire sampling period was computed by summing up each

minute's EE estimated from the corresponding HR. As all the subjects were wearing HR monitor for about, but not exactly, 16 hours, the total energy expenditure over the sampling period was adjusted to a period of 16 hours, so as to remove the effect of different lengths of monitoring periods. TEE_{16h} = (960/time) * TEE, whereas TEE_{16h} (KJ/16h) is total EE over 16 hours; time (minutes) is the length of wearing HR monitor; and TEE (KJ/sampling period) is the total EE over the whole monitoring period.

Statistical analysis

In order to analyze the variation of the logistic calibration curves, the energy expenditure estimated from a given person's minute-by-minute HR recording but using different individual calibration curves were analyzed. The intra-individual variation of the calibration curves was calculated based upon the 1st and 2nd measurement by using ANOVA, the inter-individual variation was obtained by ANOVA and corrected for the intra-individual variation. Since the individual calibration procedure based on 18 different activities is quite time- and labour- consuming, we tried to look for some other simpler calibration procedures as alternatives. One was to estimate individual EE by individual calibration procedure based on less activities, another one was to estimate individual EE by average group calibration curve, which may be obtained from the data of other studies on the same population. Therefore, the accuracies of EE using average group calibration curves and using individual calibration curves based on 9 instead of 18 mixed activities were also analyzed. The selected 9 activities were BMR, sitting and standing quietly, standing with hands movement, cycling at 0 and 30 watts, step test on a single stair and working activity in the cotton mill. To determine whether a single calibration equation could be used for all the subjects, the total group of subjects was randomly divided into two groups, A and B. The average calibration curve of group A was cross-validated in group B against the individual calibration curves based on 18 mixed activities, and vice versa. The validity of the different ways of computing an individual EE was tested by the method of Bland and Altman (13). All the analyses were done by the SPSS software program (14). Values are given as mean $\pm$ SD.

RESULTS

Characteristics of the subjects are shown in **Table 1.** On the 2nd session of the assessment, body weight was not statistically different from that on the 1st session. **Table 2** summarizes the EE and HR of each activity in the calibration procedures for the 1st and 2nd session of the assessment.

TABLE 1

Subject characteristics at the beginning of the study (n=40)

	$\bar{x}$	SD
Age (Y)	29.7	6.4
Education level (Y)	9.5	1.2
Working duration (Y)	10.6	7.0
Weight (kg)	53.3	6.4
Height (cm)	160.6	4.6
Body mass index (kg/m^2)	20.7	2.1

TABLE 2

Energy expenditure (EE) and heart rate (HR) of each activity in the calibration procedure for the 1st and 2nd session of assessment (n=40)

Activities	EE(KJ/min)		HR(beats/min)	
	1st Mean(SD)	2nd Mean(SD)	1st Mean(SD)	2nd Mean(SD)
BMR_1	3.72(0.56)	3.52(0.51)	71.7(7.6)	70.3(7.5)
BMR_2	3.72(0.53)	3.55(0.56)	70.8(8.2)	69.5(6.7)
Sitting quietly	4.71(0.58)	4.54(0.46)	80.5(8.2)	78.6(8.1)
Sit & hands movement	5.92(0.84)	5.26(0.67)	88.3(8.7)	84.9(8.4)
Sit & arms movement	6.57(1.01)	5.75(0.76)	92.1(10.2)	87.8(8.5)
Standing quietly	4.67(0.60)	4.63(0.62)	86.5(9.9)	85.7(10.0)
Stand & hands movement	5.66(0.86)	5.28(0.72)	93.5(10.0)	90.6(9.9)
Stand & arms movement	6.75(1.22)	6.15(0.81)	99.0(11.9)	96.1(10.7)
Sweeping	9.32(1.38)	8.59(1.16)	90.3(9.0)	89.1(9.1)

(Continued)

Kneebending	13.64(2.77)	13.57(2.49)	104.4(11.9)	105.2(11.7)
Cycling at 0_w	8.46(1.36)	7.68(1.30)	90.0(9.8)	88.4(9.8)
30_w	12.43(1.06)	12.37(1.36)	104.3(10.5)	103.2(9.8)
40_w	14.61(1.44)	14.30(1.47)	112.9(12.5)	111.7(12.4)
60_w	19.99(1.56)	19.62(2.19)	132.7(14.8)	128.8(14.8)
80_w	23.73(2.04)	23.02(2.11)	146.9(15.1)	144.0(16.0)
Single step	15.29(2.62)	14.89(2.02)	112.7(12.1)	112.0(10.9)
Multiple steps	19.90(3.57)	19.84(2.51)	127.5(16.3)	125.9(13.1)
Job activities	9.02(1.59)	8.45(1.56)	102.6(11.5)	99.8(11.0)

BMR_1 and BMR_2 were the first and the second measurement of basal metabolic rate on each occasion.

In this study, the calibration curves of EE versus HR fit logistic function well, the squared multiple correlation coefficient (R^2) was 0.91 $\pm$ 0.06 (mean $\pm$ SD) (n=40). **Figure 1** gives an example of a typical calibration curve, the individual curves were however quite different from one to another.

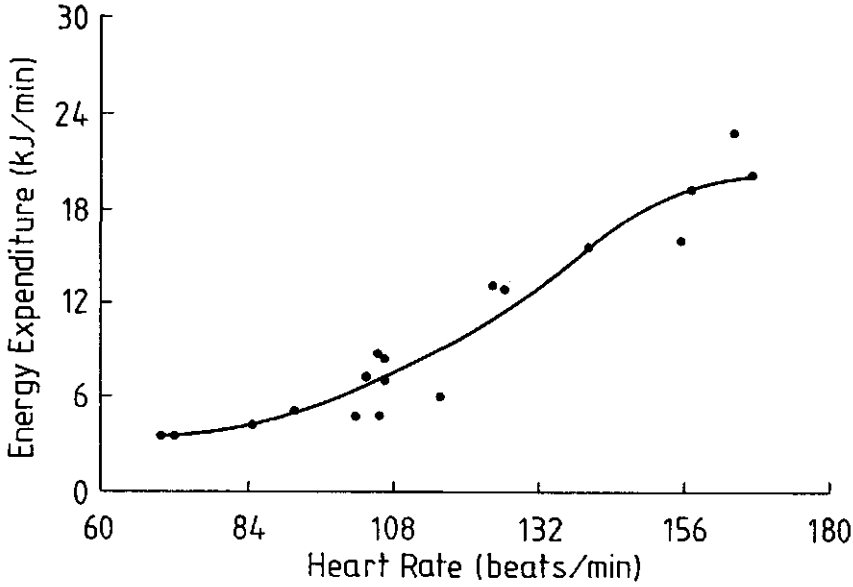

FIG 1. A regression line between energy expenditure and heart rate obtained from the calibration procedure of one subject (multiple R^2=0.91, $p<0.001$).

Since a logistic calibration curve has no single slope or intercept to be compared, on the other hand the information on EE estimated from HR by referring to such line is more meaningful, we apply a selected person's HR data to all the 40 different individual logistic calibration curves to analyze the variation in the relationship between HR and EE. Since the change of EE is not proportional to HR in the lower part of logistic curve as the higher part, we selected two persons with different distribution of HR, one with higher average HR, another one with lower average HR, for calculating

EE. **Table 3** shows that the coefficients of inter- (CV_{inter}) and intra-individual variation (CV_{intra}) of calibration curves were large both at high HR and at low HR levels.

TABLE 3

Inter- and Intra-individual variation in the relation between energy expenditure (EE) and heart rate (HR) (n=40)*.

	EE (KJ/16h)		CV(%)†	
	Mean	SD	CV_{inter}	CV_{intra}
A person's HR data with higher average ($\bar{x}$=106.6 beats/min) was applied to different calibration curves				
1st session of individual curves based on 18 activities	12271	2262	17.4	
				10.6
2nd session of individual curves based on 18 activities	12143	2264	17.6	
1st session of individual curves based on 9 activities	11428	2574	14.5	
				20.4
2nd session of individual curves based on 9 activities	11885	2678	13.9	
A person's HR data with lower average($\bar{x}$=74.3 beats/min) was applied to different calibration curves				
1st session of individual curves based on 18 activities	4996	735	14.1	
				11.4
2nd session of individual curves based on 18 activities	4755	886	14.8	
1st session of individual curves based on 9 activities	4499	820	15.1	
				13.6
2nd session of individual curves based on 9 activities	4548	866	14.9	

* Mean values of EE were calculated from individual calibration curves, but based on one given person's free living HR.

† CV, coefficient of variation.

Figure 2 shows the repeatability of individual curves on the basis of 18 activities obtained from two sessions of the assessment with a 12 weeks interval. Only session 1 individual free living HR recording was used to estimate EE, but with reference to both session 1 and session 2 individual calibration curves. The mean difference in EE from repeated assessment of individual curves is -124 KJ/16h with a standard deviation of 1431 KJ/16h.

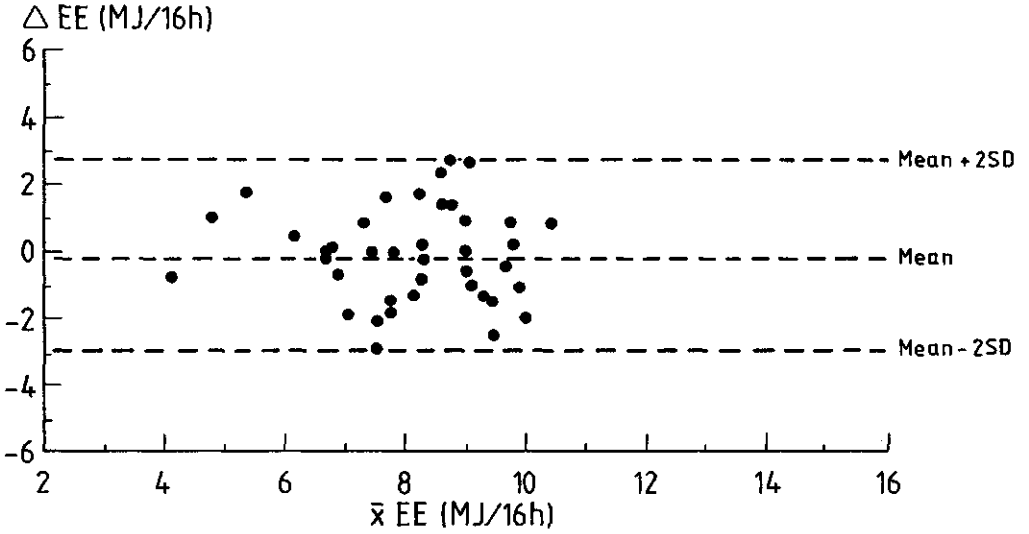

FIG 2. Individual difference in energy expenditure between the first and the second measurement (ΔEE) in relation to the mean energy expenditure of two measurement (x̄EE). (Each point is one of the 40 subjects tested. Individual energy expenditure was calculated using session 1 and session 2 individual calibration curves, but using only session 1 individual free living heart rate data.)

Table 4 compares the different ways of computing EE. EE estimated using individual calibration curves containing 18 mixed activities was used as a standard, which was compared with the EE using the average calibration curve of the group and with the EE using individual curves containing only 9 mixed activities. Individual minute-by-minute HR recording was used for the fore-mentioned comparison.

TABLE 4

The comparison of energy expenditure (EE) estimated from individual minute-by-minute heart rate recording between using different calibration curves

	EE(KJ/16h)		Difference(KJ/16h)*
	Mean	SD	Mean ± SD (range)
The first session:			
Individual curves based on 18 activities (n=40)	8172	1630	
1. Individual curves based on 9 activities (n=40)	7882	2075	-290 ± 1054 (-3801,+2543)
2. Group A curve (n=21)	8044	1544	-589 ± 1547 (-3986,+2097)
3. Group B curve (n=19)	7803	198	+141 ± 2425 (-3532,+5034)
The second session:			
Individual curves based on 18 activities (n=40)	8049	1568	
1. Individual curves based on 9 activities (n=40)	7999	1509	-50 ± 785 (-1535,+1852)
2. Group A curve (n=21)	7998	1536	-221± 1336 (-2401,+2071)
3. Group B curve (n=19)	7807	2057	-53 ± 2848 (-5148,+5544)

* The mean difference in EE was calculated from individual curves based on 18 activities or calculated from other types of curves, parenthesis represent the lowest and the highest individual differences

For the 1st session of the study, the mean difference in EE between using individual calibration curves and using the mean calibration curves of group A or group B were -589 and +141 KJ/16h respectively, whereas the individual discrepancies ranged from -3986 to 2097 KJ/16h and from -3532 to 5034 KJ/16h respectively. The mean difference in EE when using individual calibration curves based on 18 and 9 mixed activities was -290 KJ/16h, whereas the individual discrepancies were much larger (between -3801 and 2543 KJ/16h). For the second study of the assessment, the results were similar.

Figure 3 plots the individual differences in EE estimated from individual HR recording between using an average group curve and individual calibration curves based on 18 activities. The limits of agreement in EE between using individual curves and group curves (mean difference $\pm$ 2 SD) were from -3683 to 2505 KJ/16h for using the average curve of group A, and from -4709 to 4991 KJ/16h for using the average curve of group B.

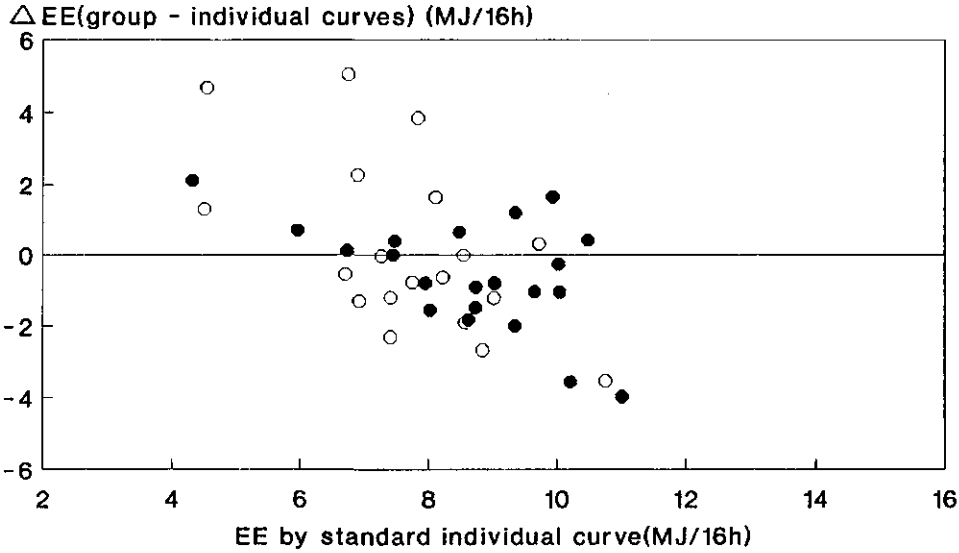

FIG 3. Individual difference in energy expenditure using individual calibration curves based on 18 activities or using average group calibration curves (ΔEE) in relation to the energy expenditure using individual calibration curves base on 18 activities. (Individual calibration curves based on 18 activities is used as a standard. Average group curve was obtained from the mean value of EE and HR for the whole group. ● and ○ represent each subject's difference in EE using her own calibration curve or using an average curve of group A or group B respectively.)

Figure 4 plots the individual differences in EE estimated from individual HR recording between using individual calibration curves based on 9 and 18 activities.

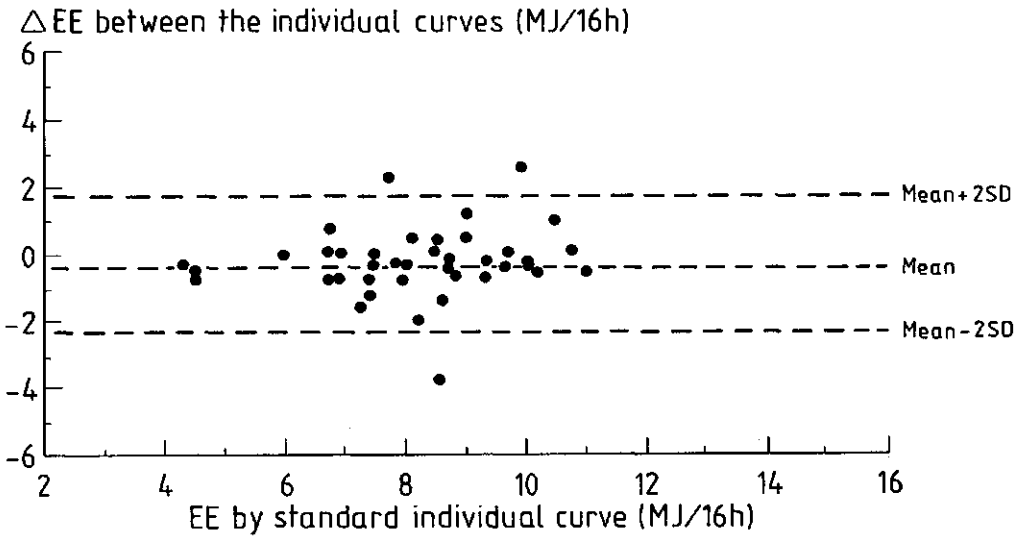

FIG 4. Individual difference in energy expenditure calculated from individual calibration curve based on 18 or based on 9 levels of activities (ΔEE) in relation to individual energy expenditure calculated from individual calibration curve based on 18 activities. (Individual calibration curves based on 18 activities is used as a standard.)

DISCUSSION

The estimation of EE from HR monitoring, which was introduced years ago (1,4,15), was recently validated against indirect calorimetry (7), against the doubly labelled water technique (8,9,16) and against energy intake adjusted for changes in body energy stores (17). A potential criticism on these validating studies is that HR method favours good results by using the same type of exercise during calibration and test periods. A lot of information is available documenting the influence of the type of activity and posture on the relationship between EE and HR (18,19). **Table 2** also provide evidence that the heart rate in all the three standing positions was higher than in counterpart sitting positions, although the EE were similar. Therefore calibration procedures must be representative for every day life. In the current study, the calibration procedure consists of a variety of different activities simulating both posture and movements during habitual life. Although this may result in a decrease in correlation coefficients, it has a greater applicability to real daily life. Calibrating difficulties were also observed in measuring the resting and light activities when considerable variations in HR may be encountered, which however are not accompanied by proportional changes in EE. In order to cope with this problem, two separated lines have been used to estimate EE in the previous Flex HR methods (20,21). The problem of this approach is that the accuracy of the final results heavily depend on the appropriateness of the Flex HR value (an individually predetermined HR that can be used to discriminate between resting and exercise HR). In present study, logistic regression curves were calculated to fit the calibrating points. The curves were constrained to pass through the lower calibration points and reflect the phenomenon that the variation in HR may not be parallel to the change in EE under light activities as it does under moderate activities.

The variation of the logistic calibration curves was analyzed as the EE was estimated from a given person's HR but using different individual calibration curves. Both the coefficients of inter- and intra-individual variation of the relationship between EE and HR were large, ranging from 14.1% to 17.6% and from 10.6% to 20.4% respectively (**Table 3**). In the long term the variation in the relationship between EE and HR may be affected by physiological factors such as changes in body weight or body

composition, state of training, illness or aging. In the short term such variation may be due to minor infection or insufficient sleep (22), environment temperature (23), emotion (24), the consumption of alcohol or caffeine or smoking of cigarettes (25), time after consumption of the meal (26) and different type and intensity of activities (20,21,27). Therefore the individual calibration curve should be used and should be generated for different situations, in order to provide a close estimation of an individual's EE from HR recording. It needs to be stressed that even in the single individual the calibration curve may change greatly from one occasion to another. Although the mean difference in EE from repeated assessment of individual curves was small (-124 KJ/16h)), individual difference ranged from -2986 KJ/16h to +2738 KJ/16h (**Figure 2**). This implies that when the calibration curves of one occasion are applied to another, the EE may be over-estimated by 2738 KJ/16h or under-estimated by 2986 KJ/16h. Therefore it is necessary to develop the individual calibration curves immediately prior to the HR recording period. In Figure 2, although three subjects have very low EEs, but they were reproducible for the second measurement as ΔEEs of these three subjects were within the 'limits of agreement', defined as the mean difference ± 2SD. The reasons for such lower EEs could be due to either only 16 hours of EE was estimated or the sizes of three subjects were smaller (The heights for these three subjects were 156.2, 154.9 and 157.1 cm respectively; the weights for these three subjects were 37.7, 48.2 and 45.6 Kg respectively.

This study also compared the different ways of computing EE from HR recording. For single individuals, discrepancies in the order of -3986 to 5034 KJ/16h or -3801 to 2543 KJ/16h were obtained when using average group calibration curves or using individual curves containing limited activities respectively (**Table 4**). The poor limits of agreement between average group calibration curves and individual curves further support the point that the estimation of individual EE from HR recording can only be based on individual calibration procedures (**Figure 3**). Since the 'limits of agreement' between individual calibration curves based on 9 or 18 activities were found to be from -2399 KJ/16h to 1817 KJ/16h (**Figure 4**), individual calibration curves based on only 9 activities may be unacceptable.

In summary, although a relation exists between EE and HR, this relation differs between individuals and within individuals under different occasions. If this relation is

to be used to predict habitual EE, the estimation of individual EE from HR recording should be based on individual calibration procedure containing as many different activities as possible. It needs to be stressed that even in the same individual, the calibration procedure needs to be repeated on different occasions.

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CHAPTER 4

Functional Consequences of Iron Supplementation to Iron Deficient Female Cotton Mill Workers in Beijing, China

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ABSTRACT

80 iron deficient, non-pregnant female cotton mill workers aged between 19 and 44 years were randomly assigned to ferrous sulphate (60 or 120 mg of iron/d) or placebo treatment for 12 weeks, in order to investigate the functional consequences of iron supplementation. Energy expenditure at work (EEW) and during leisure time (EEL) were estimated on the basis of minute-by-minute heart rate (HR), which was recorded in free-living conditions over 3 days. Individual calibration curves were used. Production efficiency (PE) was calculated as the ratio of productivity accomplished to energy expended. In the iron treated group, the mean haemoglobin (Hb) value increased from 114 to 127 g/l ($p<0.001$) and serum ferritin increased from 9.7 to 30.0 ug/l ($p<0.001$); while the mean free erythrocyte protoporphyrin level decreased from 570 to 277 ug/l ($p<0.001$). As a result of the iron supplementation, mean heart rate at work decreased from 95.5 to 91.1 beats/min ($p<0.001$). This change was inversely correlated with the

change in Hb value ($r=-0.60$, $p<0.001$). EEW decreased on average by 467 KJ/d in the iron treated women ($p<0.001$) and slightly increased by 71 KJ/d in the placebo group ($p>0.05$). PE significantly increased by 18% in the iron treated group ($p<0.001$) and its change parallelled the change in Hb value ($r=0.58$, $p<0.001$). These results show that iron supplementation enabled these women to do the same work at a lower energy cost, and could reduce cardiovascular stress.

INTRODUCTION

Previous studies, conducted by the Chinese Academy of Preventive Medicine (1), showed a high prevalence of anaemia among Chinese women. The predominating type of anaemia in this population was found to be iron deficiency. There are indications in the literature that the productivity of anaemic workers is reduced. Basta et al (2) found a correlation between haemoglobin (Hb) level and work output in Indonesian rubber tappers. Iron supplementation significantly improved the work output. Similar observations have been obtained on tea plantations in Indonesia (3) and in Sri Lanka (4-7). An important problem with this kind of studies is that the nutritional status is not the only determinant of productivity. Motivating incentives could also have an effect on the effort expended. Weaker people could achieve the same productivity as stronger ones by spending more energy at work. In order to cope with this problem, the present study conducted from 1989 to 1991 in Beijing, China, was designed to investigate the functional consequences of iron supplementation in iron deficient female cotton mill workers, with emphasis on heart rate (HR), energy expenditure at work (EEW), energy expenditure during leisure time (EEL) and production efficiency (PE).

SUBJECTS AND METHODS

Subjects

447 female workers in a cotton mill in Beijing underwent a screening test for anaemia. 83 non-pregnant women with a diagnosis of iron deficiency, between the ages of 19 and 44 years, were selected on the basis of this screening test and after a routine medical check-up. Three subjects dropped out of the study. One subject was not willing to participate in the intervention study, one became pregnant and one resigned from the job. Finally the data of 80 subjects were used in statistical analysis. The subjects were classified as iron deficient (ID) or iron deficient anaemic (IDA) according to the following categories (8,9): When haemoglobin (Hb) level was normal ($\geq$ 120 g/l), but the values of serum ferritin (SF) were below 12.0 ug/l and free erythrocyte protoporphyrin (FEP) were above 350 ug/l, the subject was classified as iron deficient. Iron deficiency anaemia was regarded as being present when the Hb concentration was below 120 g/l and either SF was below 12.0 ug/l or FEP was above 350 ug/l . Based on these criteria, 36 women were classified as having ID, 34 women as having mild IDA ($100 < Hb < 120$) and 10 women as having moderate IDA ($70 < Hb < 100$).

The selected ID and IDA subjects were randomly divided into two groups and then treated for 12 weeks with either iron or placebo. At the beginning and at the end of the study, all the subjects slept for one night in the factory hospital. The next day at 6:30 hours, basal metabolic rate (BMR) and HR were determined. Body weight (BW), height (HT) and fat free mass (FFM) were measured and capillary blood was collected in the fasting state and after voiding. After this, the women received a standard breakfast containing about 2100 KJ. About 30 minutes after breakfast, the calibration procedure involving simultaneous measurements of energy expenditure (EE) and heart rate (HR) started. The subjects were asked to carry out a number of activities, similar to those commonly encountered in daily life, during which HR was recorded and EE was measured. On days before or after the calibration procedure, minute-by-minute HR and physical activities were recorded for three consecutive days. **Figure 1** summaries the study protocol.

Treatment	Pre-intervention		iron-treated(n=40) placebo(n=40)	Post-intervention	
Duration	three days	one day	-- 12 weeks --	one day	three days
Measurement	recording: HR activity	BMR BW,HT,FFM Hb,SF,FEP HR-EE Cal.		BMR BW,HT,FFM Hb,SF,FEP HR-EE Cal.	recording: HR activity

Figure 1. Study Protocol
(BMR, basal metabolic rate; HR, heart rate; BW, body weight; HT, height; FFM, fat free mass; Hb, haemoglobin; SF, serum ferritin; FEP, free erythrocyte protoporphyrin; HR-EE cal., calibration procedure).

Measurements

BMR was measured under standard conditions in a comfortably warm room, with the subject lying at complete rest after having fasted for at least 12 hours. It was determined by indirect calorimetry from two 10- minutes samples of expired air. The expired air was collected in a 100 L Douglas bag after 5 minutes of stabilization. Oxygen and carbon dioxide contents and the volum of expired air were measured by a paramagnetic oxygen analyzer (Servomex 570A, UK), an infra-red carbon dioxide analyzer (Servomex 1410, UK) and a precision wet gas meter (Schlumberger B.V., The Netherlands) respectively. Gas volumes were corrected to standard temperature and pressure (STPD).

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm respectively with a beam weighing scale and measuring system (Seca 220, Germany). The

weight of the clothes was determined separately and subtracted from the total weight. Fat free mass was estimated in duplicate by a bio-electrical impedance analyzer (BIA 101, RJL Systems, U.S.A.) as described by Lukaski et al(10). The formula provided by the manufacturer was used to estimate FFM.

Capillary blood was obtained by left ring finger stick, using disposable blood lancets (Lameris, The Netherlands). Haemoglobin was determined by the HemoCue method (11). Serum ferritin was determined with a commercially available enzyme immuno assay kit (Ramco Laboratories,INC., USA) (12), and with a Titertek Multiskan R spectrophotometer (EFLAB, Finland). Free erythrocyte protoporphyrin was determined by fluorescence spectrophotometry (DaoJin, 12F-510, Japan)(13).

Energy expenditure at work (EEW) and during leisure time (EEL)

1. Calibration procedure

Energy expenditure was estimated using the minute-by-minute heart rate monitoring method. The method is based on the relationship between HR and EE (14-17). In order to determine this relationship, individual calibration curves were generated both before and after treatment on the same day as BMR was measured. The procedure included 18 different activities simulating the posture and movements of habitual life, which is described in detail elsewhere (Li, Deurenberg, Hautvast, unpublished observations 1992). After a equilibration period of about 3 minutes, EE and HR were determined simultaneously using the Douglas bag technique and the HR monitor for 3 to 5 minutes of each activity.

2. Heart rate monitoring

Minute-by-minute HR was recorded in free living situations on three consecutive days just before or after the calibration procedure was performed. Each subject was fitted with the HR monitor (sport tester TM, PE-3000, Polar Electro, Finland) early in the morning. It was worn until it was removed by the subject before going to the bed in the

evening.

3. Calculation of energy expenditure at work (EEW) and energy expenditure during leisure time (EEL)

18 points of HR (beats/min) and EE (KJ/min) were obtained from the calibration procedure. A logistic regression line between EE and HR was generated (18). EE of every minute in the monitoring period was then calculated from the corresponding HR using each individual's HR-EE regression line. EEW and EEL of each day were computed by adding the estimated EE of each minute. The mean values of three days were used in statistical analysis.

Production efficiency (PE)

All the subjects of this study were working in a cotton mill as either operator or doffer. Their working activities were monotonous consisting mainly of hand and arm movements while walking along the machines, to join the ends of torn yarn, change the rove, clean the machine and take off the spindles when they were full of yarn. The evaluation of the productivity of the workers is based upon the quantity and quality of the yarn produced daily, which in turn determines the pay the workers receive. For the simplicity of the description, the pay of the subjects was used as an indicator of their productivity, i.e. productivity (Yuan/day) was the pay during the month before or after the intervention divided by the number of days of work during that month. Since the running pace of the machine in the cotton mill is fixed, large differences in the productivity after intervention were not expected. Therefore production efficiency (PE) is used to reflect the functional consequences of iron supplementation: PE(Yuan/MJ) = productivity(Yuan/d) / EEW(MJ/d).

Physical activity diary

The normal daily physical activities were classified into 11 types. Three observers were selected from the same workshop as the subjects. They were familiar with the subjects and were trained for two weeks to learn how to distinguish different types of activities and the time spent in these activities and how to connect the heart rate monitor. During working hours, each observer followed one subject to fill in the minute-by-minute physical activity diary and to check regularly if the heart rate monitor of the subject functioned normally. After work, the subjects were instructed to fill in a physical activity diary, reporting the types of activities and approximate duration of all activities they were engaged in. Detailed records were not requested from the subjects, because it could interfere with their habitual physical activity patterns.

Pill distribution

Ferrous sulphate pills, containing 60 mg iron, and placebos were manufactured by Lomapharm Medicine, Emmerthal, Germany. Both the medicine distributor and the subjects were blind to the treatment. Pills were distributed every day and consumed by subjects under supervision. ID and mild IDA subjects were given one pill per day of either iron or placebo, moderate IDA subjects were given two pills per day of either iron or placebo. During days off, the subjects took the pills at home. In case they forgot to take the pills at home, they were instructed to bring them back. The medicine distributor , therefore, knew how many pills the patients had taken totally.

Statistical analysis

All statistical analysis were done using the SPSS/PC computer programme (19,20). The results after intervention were compared with pre-treatment results by two-tailed paired Student's t test. Comparisons between the iron-treated and the placebo group were done using two-tailed two sample Student's t-test. The relations between the change of HR and PE values and the change of Hb values were analyzed using multiple stepwise regression with treatment as a dummy variable (21).

RESULTS

Some of the initial characteristics of the subjects are given in **Table 1.** There were no significant differences between iron treated group and placebo group.

Table 1
Initial characteristics of the subjects

parameters	iron treated group (n=40)		placebo group (n=40)	
	Mean	SD	Mean	SD
Age (Y)	30.5	5.9	29.7	6.4
Education level (Y)	9.6	1.4	9.5	1.2
Working duration (Y)	11.0	6.3	10.6	7.0
Weight (kg)	55.9	7.2	53.3	6.4
Height (cm)	161.1	5.7	160.6	4.6
FFM (kg)	40.3	4.4	39.3	3.7
BMI (kg/m^2)	21.6	3.2	20.7	2.1
Body fat (%)	27.6	4.2	25.9	4.2

FFM, fat free mass; BMI, body mass index.

General haematological data before and after the intervention in both iron-treated and placebo group are shown in **Table 2.** In the placebo group, 18 subjects were ID, 18 were mild IDA and 4 were moderate IDA, as against 18, 16, 6 respectively in the iron treated group. The difference in the changes of Hb values after intervention were statistically significant between the two groups ($p<0.001$), as well as the changes of SF and FEP values ($p<0.01$).

Table 2. Evaluation of haematological status of the subjects before and after 12 week treatment with either iron or placebo

Parameters	iron (N=40)		placebo (N=40)		
	Mean	SD	Mean	SD	
Haemoglobin(g/l)					
before treatment	114	15	115	14	
after treatment	127	12	113	14	
difference(95%CI)	13	12(9,17)**	-2	8(-5,1)	††
Serum ferritin (ug/l)					
before treatment	9.7	5.6	10.6	10.9	
after treatment	30.0	20.8	18.8	17.9	
difference(95%CI)	20.3	18.9(14.3,26.3)**	8.2	19.4(2.1,14.3)*	†
Free erythrocyte protoporphyrin(ug/l)					
before treatment	570	308	525	168	
after treatment	277	113	372	150	
difference(95%CI)	-296	264(-379,-213)**	-153	144(-199,-107)**	†

95 % CI, 95% confidence interval.

The values after treatment were significantly different from pretreatment results by paired t test: * $p < 0.05$ and ** $p < 0.001$.

The values are significantly different between two groups by group t test: † $p < 0.01$ and †† $p < 0.001$.

The length of HR recording at work (LengthW) and during leisure time (LengthL), mean HR at work (HRW) and during leisure time (HRL), total energy expenditure at work (EEW) , as well as total energy expenditure during leisure time (EEL) are presented in **Table 3**. As a result of iron supplementation, mean HR at work decreased significantly by 4.4 beats/min ($p<0.001$) and the total energy expenditure at work decreased by 467 KJ/d ($p<0.001$). **Figure 2** shows that the change of the mean HR at work was correlated with the change of the Hb value both in the iron-treated group and placebo group ($r=-0.60$, $p<0.001$).

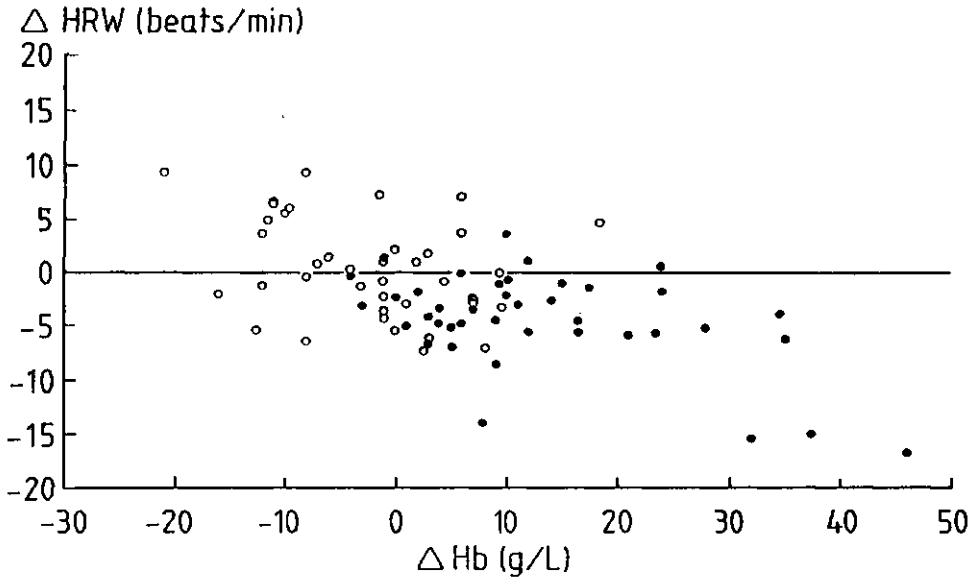

FIG 2. The change of heart rate at work (ΔHRW) against the change of haemoglobin (ΔHb) after intervention (n=80) (● and ○ represent iron-treated subjects and placebo -treated subjects respectively, $r=-0.60$, $p<0.001$).

The average productivity expressed in Chinese Yuan earned per working day and the production efficiency (PE) expressed as productivity divided by total energy expenditure at work are given in **Table 4.**

Table 4

The productivity and production efficiency (PE) of the subjects before and after 12 weeks treatment with either iron or placebo

parameters	iron treated(n=40)		placebo (n=40)	
	Mean	SD	Mean	SD
productivity(Yuan‡/day)				
before	7.34	1.09	7.44	0.51
after	7.72	0.64	7.47	0.98
difference(95%CI)	0.38	0.97(0.07_0.69)*	0.03	0.94(-0.27_0.33)
PE (Yuan/MJ)				
before	1.83	0.57	1.86	0.40
after	2.15	0.65	1.85	0.52
difference(95%CI)	0.32	0.44(0.18_0.46)**	-0.01	0.45(-0.15_0.13) †

95%CI, 95% confidence interval.

* $p<0.05$, ** $p< 0.001$: Values after treatment were significantly different from pretreatment results by paired t test.

† $p<0.001$: Values are significantly different between two groups by group t test.

‡ one Chinese Yuan was equivalent to 0.19 U.S. dollar.

Table 3

The physiological characteristics of the subjects before and after 12 weeks treatment with either iron or placebo

parameters	iron treated(n=40) Mean	SD	placebo(n=40) Mean	SD	
LengthW (minutes)					
before	440	31	444	31	
after	440	33	442	24	
difference(95%CI)	0	27(-9_+9)	-2	32(-12_+8)	
HRW (beats/min)					
before	95.5	7.6	97.6	7.3	
after	91.1	8.0	98.0	6.5	
difference(95%CI)	-4.4	4.4(-5.8_-3.0)***	0.4	4.6(-1.1_+1.9)	†††
EEW (KJ/d)					
before	4348	1204	4162	834	
after	3881	1114	4233	836	
difference(95%CI)	-467	631(-667_-268)***	71	835(-193_+335)	††

(Continued)

lengthL (minutes)					
before	377	59	391	59	
after	412	64	376	70	
difference(95%CI)	35	65(+14_+56)**	-15	74(-38_+8)	††
HRL (beats/min)					
before	86.5	8.2	89.6	5.1	
after	85.7	7.5	88.3	6.3	
difference(95%CI)	-0.8	5.7(-2.6_+1.0)	-1.3	5.5(-3.0_+0.4)	
EEL (KJ/d)					
before	2933	710	3047	888	
after	3137	827	2762	791	
difference(95%CI)	204	775(-41_+449)	-285	869(-560_-10)*	†

95%CI, 95% confidence interval; LenghthW and LengthL, the length of heart rate (HR) recording at Work and during Leisure time respectively; HRW and HRL, mean HR at Work and during Leisure time respectively; EEW and EEL, total energy expenditure at Work and during Leisure time respectively.

* $p<0.05$,** $p< 0.01$,*** $P<0.001$: Values after treatment are significantly different from pretreatment results by paired t test.

† $p<0.05$, †† $p<0.01$, ††† $p<0.001$: Values are significantly different between two groups by group t test.

When BMR was subtracted from total energy expenditure at work, PE also significantly increased from 2.77 to 3.42 Yuan/MJ in the iron treated group ($p<0.001$); whereas it slightly decreased from 2.96 to 2.81 Yuan/MJ in the placebo group ($p>0.05$). **Figure 3** shows that the improvement of PE was correlated with the increase in Hb value. Since regression analysis with the change of PE (ΔPE) as dependent variable and ΔHb, treatment, interaction factor (treatment * ΔHb) as independent variables in the two combined groups showed no treatment effect, the improvement of PE can be attributed in general by the increase in Hb value.

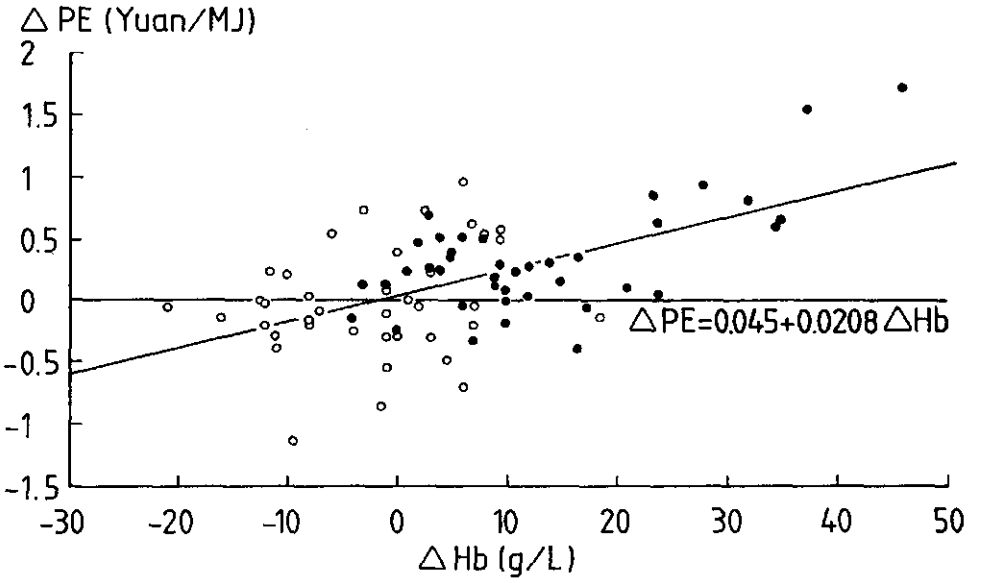

FIG 3. The change of production efficiency (ΔPE) against the change of haemoglobin (ΔHb) after intervention (● and ○ represent iron-treated subjects and placebo-treated subjects respectively, $r=0.58$, $p<0.001$).

DISCUSSION

Although none of the subjects in this study was severe anaemic, the increase in Hb value in the iron treated group was significant, while the Hb value in the placebo group did not change. The changes in SF and FEP were significant both in the iron treated group and the placebo group, but the changes in the iron treated group were much more pronounced compared to the placebo group. The reason for the small change in SF and FEP in the placebo group may be due to the fact that a programme on nutrition education given in combination with the project could have influenced the subjects to pay more attention to their food intake.

The results in Table 3 show that iron treatment decreased mean HR at work (HRW) by 4.4 beats/min, whereas no change occurred in the placebo group. The present finding is comparable to some laboratory demonstrations of HR changes during exercise in both iron deficiency and iron deficiency anaemia subjects (6,22,23). The decrease in mean HR at work was correlated with the increase in Hb value, which suggests less cardiovascular stress in the subjects with improved iron status. Although this average decrease is only 5% of mean HR at work, it implies that the frequency of higher HR during work was reduced especially.

As a result of iron supplementation, the total energy expenditure at work (EEW) was reduced by 467 KJ/d ($p<0.001$), whereas no change occurred in women receiving placebo treatment. This functional consequence is of important physiological significance, as it may enable workers to accomplish their tasks without undue fatigue. Although the total energy expenditure during leisure time (EEL) did not significantly change in the iron treated group after intervention, the difference in the change in EEL between the two groups is significant ($p<0.05$) and EEL in the iron treated group relatively increased. Therefore, at the end of the working day, the workers with improved iron status might be left with sufficient vigour to enjoy their leisure time. The analysis of the physical activity diary also revealed that the iron treated women spent about 30 minutes more time in their kitchen and in shopping after intervention (data not shown).

Since the work pace in the cotton mill is determined by the machine, the workload on the subjects after treatment was the same as before. Therefore, it may be concluded from the present findings that there was less cardiovascular stress and less exertion to do the same work after the iron status was improved.

It has been reported that both iron deficiency and iron deficiency anaemia could reduce the productivity of workers (2,3,5-7). However the productivity may not only be influenced by nutritional status, but may also be interfered with many other factors. Highly motivated, weaker people can achieve the same productivity as stronger ones by spending more energy at work. Therefore production efficiency expressed as the ratio of productivity to energy expended is probably a more objective indicator of the improvement of nutritional status. It was found that iron supplementation did reduce the energy cost of treadmill running in malnourished children (24). Diaz et al (25) also showed that energy deficient workers can maintain maximal productivity if sufficiently motivated, but at the expense of body weight. the present study investigated for the first time the effect of iron supplementation on both total energy expended at work and production efficiency.

Textile work is a continuous work at a moderate intensity, as demonstrated by the difficulties in differentiating the HR during working activity and rest period. This type of work may overtax the physical work capacity of the textile workers, particularly those with poor nutritional status, more than work requiring higher peak workloads but with relatively long rest periods in between. The present study verifies that a minimal decrease in Hb value or even non-anaemic iron deficiency could deteriorate the aerobic metabolism of female cotton mill workers enough to affect their physical work capacity. Since the work pace in the cotton mill was determined by machines, the productivity, expressed as the pay of the workers, was not improved after iron supplementation as significantly as in the rubber workers in Indonesia (2). However, the production efficiency significantly increased by 18% in the iron-treated groups, whereas it was almost constant in the placebo-treated group. The change of production efficiency after treatment was significantly correlated with the change of Hb values but not with the change of mean HR at work, which suggests that the improvement of production efficiency could not be explained directly by the decrease of mean HR at work. A possible explanation is that the specific activities of the iron-containing enzymes in the

mitochondrial electron transport system and the muscular efficiency increase with the improvement of iron status (26-30). The increased production efficiency after iron supplementation is important in the light of its potential economic impact. In this study the change in PE can be predicted from the change in Hb (Figure 3). Theoretically, an increase of 10 g/l in Hb improves PE by 14%. Because the cost of iron tablets is low compared to the economic benefits, and moreover health benefits cannot be expressed satisfactorily in financial terms, the positive cost-benefit effects of iron supplementation to iron deficient female workers may be apparent.

In summary, the present data illustrate that iron deficiency has deleterious functional consequences and impairs energy expenditure over a long period of work. After iron supplementation mean HR and energy expenditure at work were reduced and production efficiency was increased. This indicates less cardiovascular stress and less exertion with the improvement of iron status, and energy is conserved while doing the same work. These functional consequences are potentially of great importance socially and economically, especially in developing countries.

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CHAPTER 5

The Effect of Iron Supplementation on Physical Performance in Iron Deficient Females during Exercise

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ABSTRACT

In order to investigate the physical performance during experimental exercises before and after 12 weeks of iron supplementation in marginal iron deficiency anaemic women, 80 subjects with a diagnosis of iron deficiency were randomly assigned to ferrous sulphate (60 or 120 mg of iron/d) or placebo treatment. The experimental exercises were performed on a cycle ergometer against variable resistance. The physical performance was assessed by determing heart rate (HR), ventilation, $\dot{V}O_{2max}$ and muscular efficiency under standardized submaximal workloads. In the iron treated group, the mean values of haemoglobin and serum ferritin increased 13 g/l and 20.3 ug/l respectively, while the mean free erythrocyte protoporphyrin level decreased 293 ug/l ($p < 0.001$). These changes in the iron treated group were much more pronounced than in the placebo group. As a result of the iron supplementation, the mean HR was significantly decreased at 4 out of 5 different workloads of cycling and the mean ventilation was significantly reduced mainly at heavier workloads of cycling. The effect on $\dot{V}O_{2max}$ was not evident in marginal

iron deficient anaemic subjects, but they may perform the same submaximal tasks at a higher percentage of their maximal work capacity as shown by significantly increased gross and net muscular efficiency after iron treatment. It is concluded that marginal iron deficiency may not limit the maximal physical work capacity, but it may cause impairment of prolonged submaximal physical performance.

INTRODUCTION

Although there is little doubt about the physiological and economic handicaps of severe iron deficiency anaemia, the consequences of the more commonly occurring marginal iron deficiency anaemia are somewhat uncertain (Perkkiö et al., 1985). Our previous study in female cotton mill workers indicates that marginal iron deficiency anaemia has deleterious functional consequences. It was found that, with the improvement of iron status, cardiovascular stress was reduced and total energy expenditure at work was conserved while doing the same work (Li et al., submitted, 1992a). Since the results of field studies can be complicated by social, economic, and motivational factors, the present investigation was performed under more controlled conditions. The specific aim was to assess the physical performance during experimental exercise before and after 12 weeks of iron supplementation in women with marginal iron deficiency anaemia. Studies of this type may be particularly important in developing countries, where iron deficiency anaemia is widespread and the economy heavily depend on manual work.

SUBJECTS AND METHODS

Subjects

83 non-pregnant women aged between 19 to 45 years, with a diagnosis of iron deficiency from an anaemia screening test, were selected for this study. The selection procedure and criteria are presented elsewhere (Li et al., 1992b). Three subjects dropped out of the study. One subject was not willing to participate in the intervention study, one became pregnant and one resigned from the job. Finally the data of 80 subjects were used in the statistical analysis. Some initial characteristics of the subjects are given in **Table 1**. The subjects were randomly divided into two groups and then treated for 12 weeks with either iron or placebo. They were classified as iron deficient (ID) or iron deficient anaemic (IDA) according to the following criteria (Cook, 1982; DeMaeyer et al., 1989): When haemoglobin (Hb) level was normal ($\geq$ 120 g/l), but the values of serum ferritin (SF) were below 12.0 ug/l and free erythrocyte protoporphyrin (FEP) were above 350 ug/l, the subject was classified as iron deficient. Iron deficiency anaemia was diagnosed as being present when the Hb concentration was below 120 g/l and either SF was below 12.0 ug/l or FEP was above 350 ug/l. None of the subjects in this study was severe IDA (Hb<70 g/l). In the placebo group, 18 subjects were ID, 18 were mild IDA (100 g/l < Hb < 120 g/l) and 4 were moderate IDA (70 g/l < Hb < 100 g/l), as against 18, 16, 6 respectively in the iron treated group.

Measurements

Before and after the 12 week's intervention, all the subjects slept for one night in the factory hospital. The next day at 6:30 hours, basal metabolic rate (BMR) and heart rate (HR) were determined. Body weight (BW), height (HT) and fat free mass (FFM) were measured and capillary blood was collected in the fasting state and after voiding. About 90 minutes after a standard breakfast containing about 2100 KJ, the subjects

exercised on a cycle ergometer (Monark 818E, Sweden) at 5 different workloads (0, 30, 40, 60 and 80 watt).

BMR was measured under standard conditions in a comfortably warm room, with the subject lying at complete rest after having fasted for at least 12 hours. It was determined by indirect calorimetry from two 10- minutes samples of expired air. The expired air was collected in a 100 L Douglas bag after 5 minutes of stabilization. Oxygen and carbon dioxide contents and the volume of expired air were measured by a paramagnetic oxygen analyzer (Servomex 570A, UK), an infra-red carbon dioxide analyzer (Servomex 1410, UK) and a precision wet gas meter (Schlumberger B.V., The Netherlands) respectively. Gas volumes were corrected to standard temperature and pressure (STPD). The oxygen and carbon dioxide analyzers were calibrated with gas mixture of known concentration each day before the measurement. The details of the procedures have been described previously (Weir, 1949; Consolazo, Johnson & Pecora, 1963).

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm respectively with a beam weighing scale and measuring system (Seca 220, Germany). The weight of the clothes was determined separately and subtracted from total weight. Bio-electrical impedance was measured as described by Lukaski et al (1986) (BIA 101, RJL Systems, USA). The formula provided by the manufacturer was used to calculate FFM.

Capillary blood was obtained by left ring finger stick, using disposable blood lancets (Lameris, The Netherlands). Haemoglobin was determined in duplicate by the HemoCue method (Laifer, Kuller & Hill, 1990). Serum ferritin was determined in duplicate (Li, Humbert & Cheng, 1978) with a commercially available enzyme immuno assay kit (Ramco Laboratories,INC., USA), and with a Titertek Multiskan R spectrophotometer (EFLAB, Finland). Free erythrocyte protoporphyrin was determined by fluorescence spectrophotometry (DaoJin, 12F-510, Japan) with some modification (Piomelli, Brickman & Carlos, 1976; Chen, 1981).

The experimental exercises were performed on a mechanically braked cycle ergometer. The height of the saddle on the ergometer was adjusted to each individual to ensure a slight bending of the knee when the anterior part of the foot was placed on the pedal in its lowest position . The pedal rate was kept constant using a metronome

(Taktell, Germany). Cycling under 0 watt was at 30 revolutions per min. Cycling at 30 and 60 watts and at 40 and 80 watts were continued at 30 and 40 rpm respectively. To achieve a steady rate, the duration of exercise at each workload of cycling lasted for about 6 min. During the last 3 minutes at each workload, expired air was collected. Gas analyses were performed in the same way as for the BMR measurement. Simultaneously with the exercise the minute-by-minute HR was recorded continuously (Sport Tester™ PE 3000, Polar Electro, Finland). Rest intervals of 10 to 40 minutes between exercise bouts were allowed for HR and respiration to reach resting levels again.

Pill distribution

Ferrous sulphate pills containing 60 mg iron and placebos were provided by Lomapharm Medicine, Emmerthal, Germany. Both pill distributor and the subjects were blind to the treatment. Pills were distributed every day for 12 weeks to each subject and taken under supervision. ID and mild IDA subjects were given one pill per day of either iron or placebo, moderate IDA subjects were given two pills per day of either iron or placebo. During the days off (two of eight days), the subjects took the pills at home. In case they would forget to take the pills at home, they were instructed to bring them back.

Statistical analysis

The relationship between heart rate and oxygen uptake on the cycle ergometer was calculated by linear regression analysis. The maximal oxygen uptake ($\dot{V}O_{2max}$) was calculated to evaluate the physical work capacity. It was predicted by extrapolation of the linear line to the subjects' presumed maximal heart rate (220 - age) (Åstrand & Rodahl, 1986). The data obtained from each subject on the cycle ergometer were used to calculate cycling efficiency using different definitions:
1). Gross efficiency = caloric equivalent work accomplished(W)/energy expended(EE); 2). Net efficiency = W/(EE-BMR); 3). Delta efficiency = increment in work performed above the previous one(ΔW)/increment in caloric output above that at previous

workload(ΔE).

Since the relationship between caloric output and workload is essentially linear with a constant slope (Gaesser & Brooks, 1975), delta efficiency was calculated as 1/slope. The results after intervention were compared with the pre-treatment values by two-tailed paired Student's t test. Comparisons between iron-treated group and placebo group were made using two-tailed two sample Student's t test. All statistical analyses were done using the SPSS/PC$^+$ programme (1988).

RESULTS

Some of the initial characteristics of the subjects are given in **Table 1.** There were no significant differences between iron-treated group and placebo group.

Table 1
Initial characteristics of the subjects

parameters	Iron treated group (n=40)		Placebo group (n=40)	
	Mean	SD	Mean	SD
Age (Y)	30.5	5.9	29.7	6.4
Weight (kg)	55.9	7.2	53.3	6.4
Height (cm)	161.1	5.7	160.6	4.6
BMI (kg/m^2)	21.6	3.2	20.7	2.1
FFM (kg)	40.3	4.4	39.3	3.7
Body fat (%)	27.6	4.2	25.9	4.2

BMI, body mass index; FFM, fat free mass.

In the iron treated group, the mean haemoglobin value increased from 114 to 127 g/l, serum ferritin increased from 9.7 to 30.0 ug/l, and the mean free erythrocyte protoporphyrin level decreased from 570 to 277 ug/l ($p<0.001$). In the placebo group, the mean haemoglobin value decreased from 115 to 113 g/l ($p>0.05$), serum ferritin increased from 10.6 to 18.8 ug/l ($p<0.05$), and the mean free erythrocyte protoporphyrin level decreased from 525 to 372 ug/l ($p<0.01$). The difference in the changes of Hb values after intervention was statistically significant between the two groups ($p<0.001$), as well as the changes of SF and FEP values ($p<0.01$).

Table 2 describes the initial values and the changes of heart rate, respiratory ventilation and energy expenditure under basal condition and at 5 different workloads of cycling after intervention. In the iron-treated group, the mean heart rate and the mean energy expenditure significantly decreased at 4 out of five different workloads of cycling, whereas in the placebo group, the mean heart rate decreased only at 60 watts, and energy expenditure decreased only at 0 watt of cycling. In the iron-treated group, the mean ventilation was significantly reduced mainly at heavier workloads of cycling after intervention, whereas the mean ventilation did not change in the placebo group. The differences between iron-treated group and placebo group were, however, not statistically significant. When the data from moderate anaemic subjects were omitted in the iron-treated and placebo groups, the results were not significantly influenced.

Table 3 shows the changes of estimated maximal oxygen uptake after intervention in both iron treated and placebo groups, as well as in different subgroups. As a result of iron supplementation, the maximal oxygen uptake was significantly increased only in moderate anaemic subjects.

Table 4 gives the average gross efficiency, net efficiency and delta efficiency from the 5 different workloads of cycling, for both the iron-treated group and the placebo group, before and after intervention. In the iron-treated group, the average gross and net efficiency significantly increased, whereas in the placebo group, no changes occurred.

Table 2

Initial values and the changes of heart rate (HR), ventilation and energy expenditure (EE) under basal conditions and at 5 different workloads of cycling after intervention (Mean ± SD)

	HR (Beats/min)		Ventilation (L/min)		EE (KJ/min)	
	Initial	Change	Initial	Change	Initial	Change
Iron-treated group (n=40)						
Basic state	69.6(6.7)	-1.6(6.3)	4.87(0.79)	0.00(0.62)	3.87(0.60)	-0.20(0.49)
0 watt	89.1(9.0)	-4.2(8.8)**	9.93(2.46)	-0.77(2.32)*	8.86(1.95)	-1.16(1.78)***
30 watts	101.6(9.4)	-2.4(8.2)	12.73(3.54)	+0.30(3.54)	12.47(1.62)	-0.62(1.90)*
40 watts	109.9(11.1)	-4.4(8.8)**	15.23(2.61)	-0.44(2.57)	14.54(1.52)	-0.22(1.90)
60 watts	126.1(13.0)	-3.9(10.4)*	21.88(3.77)	-1.77(3.70)**	19.89(1.67)	-0.81(2.36)*
80 watts	143.0(15.0)	-6.7(9.7)***	26.83(4.16)	-2.28(5.65).	23.76(2.05)	-0.92(2.38)*

(Continued)

placebo group (n=40)						
Basic state	71.0(7.8)	-1.0(5.9)	4.91(1.04)	-0.28(1.00)	3.72(0.54)	-0.18(0.19)
0 watt	90.0(9.8)	-1.6(8.6)	10.20(2.26)	-0.48(1.66)	8.46(1.36)	-0.78(1.38)*
30 watts	104.3(10.5)	-1.1(8.4)	13.52(2.43)	+0.20(2.27)	12.43(1.06)	-0.06(1.38)
40 watts	112.9(12.5)	-1.2(9.0)	15.18(2.19)	-0.06(3.26)	14.61(1.44)	-0.31(1.74)
60 watts	132.7(14.8)	-3.9(11.2)*	22.46(3.25)	-0.85(3.02)	19.99(1.56)	-0.36(2.15)
80 watts	146.9(15.1)	-2.0(12.0)	27.22(4.96)	-1.07(5.73)	23.73(2.04)	-0.70(2.71)

* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$: Values after treatment are significantly different from pre-treatment results by paired t test.

Table 3.

The maximal oxygen uptake (l/min) before and after intervention (Mean ± SD)

	Maximal oxygen uptake(l/min)		
	Before	After	Change
Iron treatment			
total group(n=40)	1.87(0.34)	1.97(0.34)	+0.10(0.26)*
iron deficiency(n=18)	1.84(0.39)	1.91(0.32)	+0.07(0.27)
mild IDA(n=16)	1.95(0.27)	1.99(0.34)	+0.04(0.15)
moderate IDA(n=6)	1.74(0.32)	2.16(0.41)	+0.42(0.12)*
Placebo treatment			
total group(n=40)	1.81(0.33)	1.82(0.35)	+0.01(0.22)
iron deficiency(n=18)	1.85(0.28)	1.86(0.33)	+0.01(0.20)
mild IDA(n=18)	1.83(0.37)	1.87(0.32)	+0.04(0.28)
moderate IDA(n=4)	1.37(0.30)	1.30(0.27)	-0.07(0.04) †

IDA, iron deficiency anaemia.

* $p < 0.05$: Values after treatment are significantly different from pre-treatment results by paired t test.

† $p < 0.05$: The changes are significantly different between two groups by group t test.

Table 4.

Cycling efficiency (%) before and after intervention

	Before		After		Change	
	Mean	SD	Mean	SD	Mean	SD
Iron treated groups						
mean gross efficiency	17.39	1.39	18.26	1.43	0.87	1.74 **
mean net efficiency	22.80	2.69	23.91	2.20	1.11	3.17 *
delta efficiency	31.46	4.23	31.46	3.16	0.03	5.19
Placebo groups						
mean gross efficiency	17.54	1.36	17.90	1.70	0.32	1.68
mean net efficiency	22.67	2.14	22.81	2.17	0.07	2.79
delta efficiency	30.86	3.38	31.25	4.80	0.41	5.73

* $p < 0.05$ and ** $p < 0.01$: Values after treatment are significantly different from pre-treatment results by paired t test.

DISCUSSION

The individual's physical performance is determined by the following factors (Vellar & Hermansen, 1971): 1) energy liberation by aerobic and anaerobic processes, 2) neuro-muscular function, and 3)psychological factors. In the present study, the effect of marginal iron deficiency anaemia on physical performance was assessed by measuring changes in HR, ventilation, $\dot{V}O_{2max}$ and muscular efficiency under standardized submaximal workloads of cycling after iron supplementation.

It is well accepted that maximal work performance is limited by severe anaemia (Wranne & Woodson, 1971; Viteri & Torun 1974; Davies et al, 1982). In spite of numerous investigations there is, however, still no general agreement that mild or even moderate anaemia affects exercise tolerance (Charlton et al., 1977).

Although none of the subjects in this study was severely anaemic, the increase in Hb value in the iron treated group was significant, while the Hb value in the placebo group did not change. The changes in SF and FEP were significant both in the iron treated group and the placebo group, but the changes in the iron treated group were much more pronounced than in the placebo group. The reason for the changes in SF and FEP in the placebo group may be that a programme on nutrition education given in combination with the project could have influenced the subjects to pay more attention to their food intake.

The higher HR and respiratory ventilation during exercise can be taken as evidence that physical performance is poorer (Desai et al., 1984). In the present study, HR and ventilation in the basic state were the same after intervention in both the iron-treated group and placebo group (Table 2), which suggests that marginal iron deficiency anaemia has no obvious effect on these measurements in the basic state. As a result of iron treatment, HR and ventilation during cycling exercises were significantly reduced, especially under heavier workloads, which is in agreement with previous studies (Viteri & Torun, 1974; Ohira et al, 1979). Although the changes between the iron-treated group and the placebo group did not reach statistically significant differences, the direction of

the decreases in HR and ventilation were much more in favour of the iron-treated group.

Maximal oxygen uptake has been widely used as an index of physical performance, as it gives valuable information about both the functional capacity of the oxygen transport system (haemoglobin) and the maximal work power of a subject. In order to avoid exposing the anaemic subjects to the risk of a potentially harmful exhaustion at maximal work rate, the maximal oxygen uptake ($\dot{V}O_{2max}$) was predicted from a submaximal cycle ergometer test with an extrapolation of the linear line between O_2 consumption and HR to a presumed maximal HR. The present results (Table 3) suggest that marginal iron deficiency anaemia has no effects on $\dot{V}O_{2max}$, since the predicted $\dot{V}O_{2max}$ was significantly improved only in moderately anaemic subjects after iron treatment. Work by Schoene et al (1983), Finch et al (1979, 1986), Davies et al (1982), and Vellar & Hermansen (1971) would not lead one to expect significant changes in this variable as long as Hb levels stayed within the normal or even sub-normal range. Although the indirect method may not provide the same degree of accuracy as the direct method, it gives valuable information about longitudinal changes as each individual serves as its own control.

Muscular efficiency of an individual during steady rate exercise is expressed as the ratio of work accomplished (W) to energy expended (E). It is obvious that selection of the base-line correction factor will change estimates of energy efficiency. Therefore in this study different definitions of muscular efficiency were computed. The present results suggest that the effect on $\dot{V}O_{2max}$ was not evident in marginally iron deficient anaemic subjects, but they may perform the same submaximal tasks at a higher percentage of their maximal work capacity as shown by significantly increased gross and net muscular efficiency after iron treatment (Table 4). Within the limitation imposed by the evidence of significant difference between the groups, some support is given to the work of Davies et al (1982), who concluded that it is possible to have decreased skeletal muscle oxidative capacity because of diminished or depleted iron stores per se. In iron deficiency, the concentration and activities of iron-containing electron transport protein or enzymes, including cytochrome c (McLane et al., 1981; Siimes, Refino & Dallman, 1980), α-glycerophosphate oxidase (Finch et al., 1979), succinate dehydrogenase and pyruvate-malate dehydrogenase (Davies et al., 1984; Maguire et al., 1982; McLane et al., 1981) are drastically depressed. Previous experiments (Davies et al., 1984) suggested that

concentration of Hb was a major determinant of $\dot{V}O_{2max}$, whereas mitochondrial oxidative capacity was more likely to be the limiting factor in endurance capacity. Consequently, HR and ventilation will be increased as one of the compensatory mechanism to maintain adequate tissue oxygenation (Finch & Lenfant, 1972; Woodson, Wills & Lenfant, 1978).

Since the relationships between caloric output and workload after intervention were in parallel with the ones before intervention, the calculation of delta efficiency does not seem to be an appropriate method of reflecting the change of muscular efficiency for this type of studies, although it does accurately describe the relationship between caloric output and work rate (Gaesser & Brooks, 1975).

It is concluded that marginal iron deficiency anaemia may not limit maximal physical work capacity, but it may cause impairment of prolonged submaximal physical performance.

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CHAPTER 6

General Discussion

6.1. Prevalence and type of anaemia in this population

A high prevalence of anaemia (34%) was found in Chinese female menstruating cotton mill workers and the major type of anaemia in this population was found to be iron deficiency. Low availability or utilization of iron, and excessive blood loss in intra-uterine devices (IUDs) users may be the most common risk factors leading to iron deficiency and iron deficiency anaemia in this population. Although the exact causes of iron deficiency in this population could not be determined from this study, oral iron treatment was found to be effective and iron supplementation to IUD users suffering from menorrhagia may well be beneficial (Chapter 2).

At international level, the World Health Organization proposed a value of 12.0 grams haemoglobin per 100 ml as the lower limit of normal for adult non-pregnant females (World Health Organization 1968). However, it is very difficult to define 'standard' or 'normal' values for Hb concentration, since Hb concentration depends on age, sex, pregnancy, altitude, nutritional status, different ethnicity and methods of examination (Perry et al. 1992, Cook & Finch 1979). With due caution , the mean haemoglobin value observed in this study (12.3 g/dl) is close to the lower limit of normal haemoglobin concentration and a large proportion of the study population could be regarded as anaemic.

Since the supplementation trial constitutes an important step toward defining the nature and extent of nutritional deficiency (World Health Organization 1975), the evidence that the anaemia in this population was of the iron deficiency type was actually derived from the high response to iron supplementation in the iron treated subjects.

To achieve the national goal of limiting China's population to 1.2 billion by the year 2000, the one-child-per-family policy has been implemented since 1979 with varying degrees of success. The crude birth rate in 1949 was about 40 per 1000 population and it dropped dramatically to below 18 in 1984-1985. Since then it has slowly increased to about 21 in 1986-1987, primarily due to increasing numbers of women born during the 'baby boom' of the 1950's and 60's. Because of the safety, efficiency, economy and easiness of using intra-uterine devices (IUDs), such contraceptive practices are commonly employed among Chinese women. Previous studies showed that IUDs increased menstrual blood loss by between 35% and 146% (Guillebaud et al. 1976, Hefnawi 1974, Drife 1990). In the present study, the analysis did not show that using IUDs was a contributing factor for iron deficiency compared with other contraceptive practices such as pills and condom ($X^2=1.87$, $df=1$, $p>0.05$). However a significant difference in the severity of iron deficiency was found between subjects using IUDs for more than two years and for less than two years ($X^2=4.18$, $df=1$, $p<0.05$). Women wearing IUDs for less than two years showed more severe iron deficiency. It was reported that the main variable determining iron status in women is not the variation in dietary iron intake which is rather small, but the variation in menstrual-iron losses which is very marked. The probability of developing iron deficiency increases with increasing menstrual losses (Hallberg et al. 1966, Beaton et al. 1970, Cole et al. 1972). It has been estimated that American women using IUDs would need to absorb 4.78 mg iron daily from the diet to cover the requirements to 95%. From the distribution of iron requirements in those American women using IUDs, it was found that only 45% of women using IUDs can cover their iron requirements from the American diet. This diet only provided up to 1.65 mg absorbed iron and consequently 55% will sooner or later develop iron deficiency (Hallberg & Rossander-Hultén 1991). The absorption of iron from ordinary Chinese diet was assumed to be about 10 per cent (Chinese Academy of Preventive Medicine 1990). 18 mg iron intake per day recommended for Chinese women by Chinese Nutrition Society will thus provide about 1.8 mg absorbed iron, which is probably too low for women using IUDs. The recommended dietary allowance for daily iron intake in women using IUDs needs further studies.

6.2. The estimation of daily energy expenditure by heart rate method

Habitual energy expenditure (EE) of iron deficient women, both at work and at home, is of vital interest for the present study. A variety of methods (Coward 1988, Acheson et al. 1980, Bradfield 1971) have been used to investigate daily energy expenditure. Among them, the doubly labelled water technique provides an accurate estimate of the mean energy expenditure over a period of several days, requires little cooperation from the subjects and is unlikely to interfere with the subjects' normal lifestyle. However the expense of the technique limits its use in studies involving a large number of subjects (Schoeller & Van Santen 1982, Prentice et al. 1984). A physical activity diary is another method for estimating daily energy expenditure over a long period of time in which detailed time and motion records are converted to energy expenditure using subject-specific or tabulated values for the energy cost of each activity (Acheson et al. 1980, Geissler et al. 1986). This method is relatively cheap, but is of limited precision, as well as very labour intensive and intrusive. The third method is heart rate (HR) monitoring, which is relatively cheap, requires little cooperation from the subjects, is unlikely to modify activity pattern and is responsible to changes in intensity of the activity. With the development of small and light devices for minute-by-minute HR recording, computer storage of the data and the ability to examine the HR data rapidly by computer, the method has been substantially improved (Livingstone et al. 1990, 1992). The ability of the HR method to provide separate information on energy expenditure at work or at home make this method actually preferable to the doubly-labelled water method, irrespective of the cost differential. The principle of the estimation of energy expenditure from heart rate recording is that a relationship exists between HR and EE. In order to determine this relationship, a calibration procedure involving simultaneous measurement of EE and HR under different activities should be done. The habitual EE thus could be derived from the free living HR recording by referring to the calibration curve. The analysis of the variation in the calibration curves shows that, although a good relationship existed between EE and HR, it differed between individuals and within individuals under different occasions. If this relationship is to be used to predict habitual EE, the estimation of individual EE from HR recording should be based on individual calibration procedure containing as many different activities as possible. It needs to be stressed that even in the same individual, the

calibration procedure needs to be repeated under different occasions (Chapter 3).

6.3. The effect of iron deficiency on job performance

The present data illustrate that mean HR and total EE at work were reduced after iron supplementation. The results also show that production efficiency, expressed as the ratio of productivity to energy expended, increased with the improvement of iron status. These indicate less cardiovascular stress and less exertion with the improvement of iron status, and energy is conserved while doing the same work. The results provide evidence that iron deficiency has deleterious functional consequences and impairs energy expenditure over a long period of work (Chapter 4).

Theoretically, to compensate for the reduced oxygen transportation and utilization, the cardiovascular system may be adjusted, including increased cardiac output and velocity of the blood flow. The present results from field studies agree with some laboratory findings (Roy et al. 1963, Duke & Abelmann 1969, Andersen & Barkve 1970, Davies et al. 1973, Ohira et al. 1978, 1979), indicating that higher heart rate (tachycardia) is responsible for the higher cardiac output. Pulmonary ventilation is also frequently increased in anaemia (Blumgart & Altschule 1948, Sproule et al. 1960, Andersen & Barkve 1970). In agreement with these studies, the present study shows that the respiratory rate during exercise decreased in anaemic patients after iron treatment (Chapter 5). The elevated heart rate and respiration rate may allow anaemic individuals to engage in occupations demanding heavier energy expenditures, but may also impose a higher energy cost. These changes could reflect an imperfect compensation in trying to meet the demands for higher oxygen uptake.

The present study shows for the first time that, as a result of iron supplementation, the total energy expenditure on the same 8-hour work was reduced significantly. This suggests that the efficiency on the job is increased with the improvement of iron status. The change of production efficiency after treatment was significantly correlated with the change of Hb values but not with the change of mean HR at work, suggesting that the improvement of production efficiency could not be

explained completely by the decrease of mean HR at work. Such functional achievement is of important physiological significance, as it may enable workers to accomplish their tasks without undue fatigue.

Fatigue is generally defined as transient loss of work capacity resulting from preceding work. Factors determining work capacity and fatigue vary with the type of exercise performed. In daily work the oxidative capacity is, in most cases, limiting for the work output. Oxidative capacity is determined by oxygen uptake by the lung, oxygen transport to, and diffusion within the muscle cell, and the mitochondrial use of the oxygen for phosphorylation. The whole aerobic energy-yielding process could be impaired in iron deficiency anaemia. Therefore, anaerobic energy-yielding processes would be more depended upon, with risk of depletion of the glycogen stores and a build-up of lactate and hydrogen ions (Mognoni et al. 1990, Ohira et al. 1979). The intracellular accumulation of H^+ ions can modify enzymes and substrate in a way that disturbs the oxidative-phosphorylation coupling and the coupling of phosphate-bond energy and muscular contraction (Hultman 1982). Increased H^+ ion content could also modify ionic composition of the adenine nucleotides and intracellular chemical equilibria. Consequently, the processes involved in muscular contraction, such as membrane polarization, crossbridge formation, muscle relaxation, will be affected, since all these processes utilize ATP as the energy source and need ionic equilibrium in muscle. These may explain at least partly why the efficiency of producing energy is reduced in iron deficiency. The increase in the effort required to do the work will produce fatigue and inhibit further work.

6.4. The effect of iron deficiency on exercise performance

It is concluded that marginal iron deficiency anaemia may not limit maximal physical work capacity of exercise, but it may cause impairment of prolonged submaximal physical performance (Chapter 5).

The results suggest that, although heart rate and respiration ventilation under sub-maximal workload on a cycle ergometer may be impaired, iron deficiency itself has no

effects on $\dot{V}O_{2max}$. The possible explanation is that anaemia mainly restricts physical performance in short-term dynamic exercise, whereas the non-erythrocyte linked biochemical consequences of iron deficiency mainly affect the ability to perform prolonged submaximal exercise.

Although it has not been demonstrated in man (Celsing et al 1988), decreased functions and/or concentrations of iron-containing proteins and enzymes in skeletal muscle were found in iron deficient animals. Evidence in non-anaemic iron-depleted rats (Finch et al. 1976, Finch et al. 1979, Galan et al. 1984, Dallman et al. 1978, Askew et al. 1981) suggests that such a decrease may only impair certain types of physical performance. Davies (1982, 1984) significantly improved the state of knowledge in this area of research by differentiating short-term and endurance types of exercise in the experimental protocol for iron deficient rats. The former is restricted by Hb levels while the latter by muscle enzymes. In other words, the reduction in endurance is independent of the decrease in Hb and $\dot{V}O_{2max}$. This is very important, since prolonged activity of the endurance type is probably more closely related to job performance and to productivity than is a brief, intense form of exercise. The improved job performance after iron supplementation, observed from this study (Chapter 4), shed further light that iron deficiency per se may impair prolonged submaximal physical work performance.

In general, the present study shows: 1) the prevalence of iron deficiency anaemia is high in Chinese female menstruating cotton mill workers; 2) oral iron supplementation was effective in the women with poor iron nutritional status; 3) physical performance, both on the job and in the laboratory tests, was improved with the improvement of iron status; and 4) marginal iron deficiency may not limit maximal physical work capacity of exercise, but it may cause measurable impairment of prolonged submaximal physical performance.

These functional achievements after iron supplementation are of great importance for social and economical development. If iron nutritional status is poor in female workers, they will not be able to altogether fulfil their important role in the home and

within the family, nor will they successfully participate in the economic development of the country. Since the cost-benefit effect is probably distinct, the incentive for committing the resources to intervention programmes should be strengthened. It is also hoped that henceforth serious attention will be given to the control of not only severe iron deficiency anaemia, but also to iron deficiency with marginal or even without anaemia.

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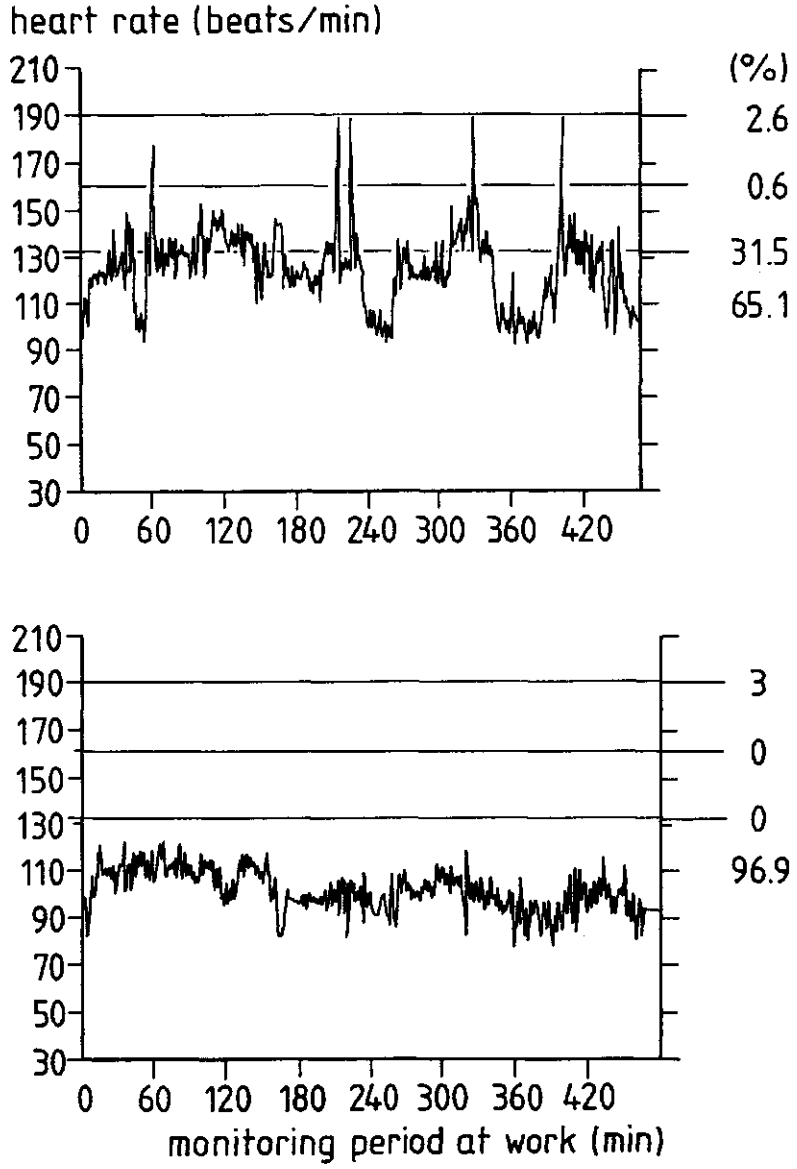
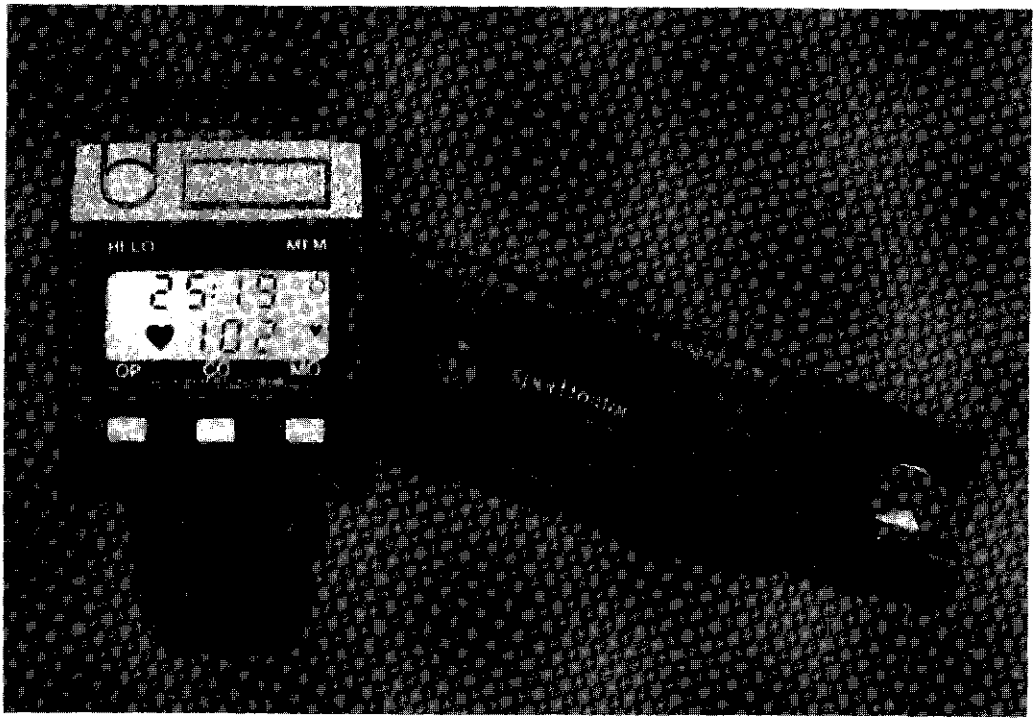
Annex I: A typical heart rate trace during work period



Note: the upper one was before iron treatment, the lower one was after iron treatment.

Annex II: Pictures



1. Mininute-by-minute heart rate monitor

2. Measuring energy expenditure during exercise

3. Collecting the expired air in the cotton mill

Summary

The general objectives of the present study were: 1) to investigate the prevalence of anaemia, its type and the contributing factors to iron deficiency in Chinese female workers; 2) to quantify the functional consequences of iron deficiency in both field and laboratory studies, with emphasis on mean heart rate at work, total energy expenditure at work, and production efficiency defined as the ratio of productivity to energy expended; 3) to identify the effect of iron deficiency per se on physical performance.

The prevalence of anaemia is reported of 447 non-pregnant female workers aged between 19 to 45 years. The World Health Organization (WHO) has proposed haemoglobin (Hb) value of 120 g/l as the lower limit of the normal range for adult non-pregnant females. The mean value of Hb in this population was 123 (SD 15) g/l and 150 out of the total 447 subjects had Hb values below 120 g/l, thus 34% of the population were anaemic according to WHO criteria. 12.0 ug/l of serum ferritin (SF) and 350 ug/l of free erythrocyte protoporphyrin (FEP) values were proposed as the lower and the higher cut-off values for iron deficiency respectively. The mean value of FEP in the total study population was 419 (SD 215) ug/l, 55% of them had FEP values higher than 350 ug/l. However, among the anaemic subjects, 72% had FEP higher than 350 ug/l. SF was tested in all the women with a Hb value less than 120 g/l and 71% of them had SF values below 12.0 ug/l.

Eighty women, diagnosed as either iron deficient or iron deficiency anaemia, were selected for a diagnostic supplementation trial. They were randomly assigned to ferrous sulphate (60 or 120 mg of iron/d) or placebo treatment for 12 weeks. Iron supplementation increased mean Hb values from 114 to 127 g/l ($p<0.001$) and mean SF levels from 9.7 to 30.0 ug/l ($p<0.001$), and decreased mean FEP values from 570 to 277 ug/l ($p<0.001$). The response rate of Hb in all the iron-treated subjects or iron treated subjects with an initial Hb below 120 g/l was 90% or 92% respectively. These findings indicate that the type of anaemia in this population was mainly iron deficiency. It was also found that in this population the severity of anaemia, not the prevalence, was significantly related to the use of intra-uterine devices (IUDs).

In order to investigate the functional consequences of iron supplementation, mean

heart rate at work (HRW), total energy expenditure at work (EEW) and production efficiency (PE) were assessed. EEW was estimated on the basis of minute-by-minute HR recording in free-living conditions over 3 days. Individual calibration curves were used, and were recalibrated again after intervention. PE was calculated as the ratio of productivity achieved to energy expended. In the iron treated group, the mean values of haemoglobin and serum ferritin increased 13 g/l and 20.3 ug/l respectively, while the mean free erythrocyte protoporphyrin level decreased 293 ug/l ($p<0.001$). These changes in the iron treated group were much more pronounced compared to the placebo group. As a result of the iron supplementation, HRW decreased from 95.5 to 91.1 beats/min ($p<0.001$). This change was inversely correlated with the change in Hb value ($r=-0.60$, $p<0.001$). EEW decreased on average by 467 KJ/d in the iron treated women ($p<0.001$) and slightly increased by 71 KJ/d in the placebo group ($p>0.05$). PE increased significantly by 18% in the iron treated group ($p<0.001$) and its change parallelled the change in Hb value ($r=0.58$, $p<0.001$). These results show that iron supplementation could reduce cardiovascular stress and enable these women to do the same work at a lower energy cost.

The physical performance during experimental exercises before and after 12 weeks of iron supplementation was also studied. The experimental exercises were performed on a cycle ergometer against variable resistance. The physical performance was assessed by determining heart rate (HR), ventilation, muscular efficiency under standardized submaximal workloads, and by estimating $\dot{V}O_{2max}$. After iron supplementation, the mean HR was significantly decreased at 4 out of 5 different workloads of cycling and the mean ventilation was significantly reduced mainly at heavier workloads of cycling. The effect on $\dot{V}O_{2max}$ was not evident in marginal iron deficient anaemic subjects. However, these subjects may perform the same submaximal tasks at a higher percentage of their maximal work capacity as indicated by significantly increased gross and net muscular efficiency after iron treatment. It may be concluded that marginal iron deficiency may not limit the maximal physical work capacity of exercise, but it may cause impairment of prolonged submaximal physical performances.

In general, the present study shows: 1) Prevalence of iron deficiency anaemia was high in Chinese female menstruating cotton mill workers; 2) Oral iron supplementation was effective in the women with poor iron nutritional status; 3) Physical performance,

both on the job and in the laboratory tests, was improved with the improvement of iron status. The total energy expenditure at work was reduced and production efficiency increased significantly after iron supplementation. 4) Marginal iron deficiency may not limit maximal physical work capacity of exercise, but it may cause impairment of prolonged submaximal physical performance.

These functional achievements with the improvement of iron status are of great importance for social and economical development in China. If iron nutritional status is poor in female workers, they will not be able to altogether fulfil their social role in the home and within the family, nor will they successfully participate in the economic development of the country. Since the cost-benefit effect is probably distinct, the incentive for committing the resources to intervention programmes should be strengthened. It is also hoped that henceforth serious attention will be given to the control of not only severe iron deficiency anaemia, but also iron deficiency with marginal or even without anaemia.

Samenvatting

De doelstellingen van de studies zoals beschreven in dit proefschrift waren: 1) de prevalentie en de soort anemie, en de etiologische factoren voor ijzerdeficiëntie in vrouwelijke Chinese fabrieksarbeiders te bestuderen; 2) de funktionele gevolgen van ijzerdeficiëntie te kwantificeren, zowel in laboratoriumstudies als ook in veldstudies, met name in relatie tot de hartfrequentie en totale energiebesteding gedurende het werk, alsmede in relatie tot de efficiëntie van energiebesteding, gedefiniëerd als de ratio van produktiviteit en energiebesteding; en 3) het effect van ijzerdeficiëntie per se op fysiek prestatievermogen te bestuderen.

De prevalentie van anemie is bepaald bij 447 niet zwangere, vrouwelijke fabrieksarbeiders, in leeftijd variërend van 19 tot 45 jaar. De Wereld Gezondheids Organisatie (WHO) hanteert voor volwassen vrouwen als laagste grenswaarde voor hemoglobine (Hb) een waarde van 120 g/l. De gemiddelde waarde van het hemoglobine in de onderzochte populatie was 123 g/l (SD 15), terwijl 150 van de 447 vrouwen een hemoglobinewaarde hadden lager dan 120 g/l. Met andere woorden, bij 34% van de populatie was er sprake van bloedarmoede volgens de criteria van de WHO. Voor serumferritine (SF) en vrij erythrocytair protoporphyrine (FEP) worden laagste respectievelijk hoogste grenswaarden bij ijzerdeficiëntie gehanteerd van 12 μg/l en 350 μg/l respectievelijk. De gemiddelde waarde van FEP in de onderzoekspopulatie was 419 μg/l (SD 215), terwijl bij 55% van de onderzochte vrouwen het gehalte aan FEP hoger was dan 350 μg/l. SF is alleen bepaald bij vrouwen met een hemoglobinegehalte lager dan 120 g/l. Bij deze groep had 71% een SF-waarde lager dan 12 μg/l.

Tachtig vrouwen bij wie hetzij een ijzergebrek, hetzij een ijzergebreksanemie was gediagnostiseerd op basis van bovenstaande criteria, werden geselecteerd voor een diagnostische interventiestudie. Zij werden random verdeeld over twee groepen die ofwel ijzer(II)sulfaat (60 of 120 mg ijzer per dag) ofwel een placebo kregen gedurende 12 weken. Ijzersupplementering verhoogde het hemoglobinegehalte van 114 g/l tot 127 g/l ($p<0.001$) terwijl de gemiddelde SF-waarde steeg van 9.7 μg/l tot 30.0 μg/l ($p<0.001$) en de FEP-waarde daalde van 570 tot 277 μg/l ($p<0.001$). De respons in het Hb-gehalte bij de personen die met ijzer behandeld werden, respectievelijk in de personen met een initiële Hb-waarde lager dan 120 g/l die met ijzer behandeld werden, was 90

respectievelijk 92%. Deze resultaten laten duidelijk zien dat het type anemie in deze populatie een gevolg is van ijzerdeficiëntie. Verder werd gevonden dat de ernst van de anemie, maar niet de prevalentie, significant gerelateerd was aan het gebruik van het intra-uterien pessarium (spiraaltje, IUD).

Om de gevolgen van ijzersupplementering op het lichamelijk funktioneren te bestuderen, werd de hartfrequentie gedurende het werk (HRW) gemeten, alsmede de totale energiebesteding gedurende het werk (EEW) en de produktie efficiëntie (PE). De hartfrequentie onder vrije leefomstandigheden werd continu geregistreerd. De energiebesteding tijdens het werk werd berekend op basis van hartfrequenties, van minuut tot minuut gemeten, gedurende een periode van drie dagen. Individuele ijkcurves werden gebruikt bij de berekening van de energiebesteding uit de hartfrequenties. Deze ijkcurves werden zowel voor als na de interventie bepaald. Produktie efficiëntie werd berekend als de ratio van produktiviteit en energiebesteding. In de met ijzer behandelde groep stegen de gemiddelde waardes van hemoglobine en serumferritine 13 g/l en 20.3 μg/l respectievelijk, terwijl de gemiddelde waarde van vrij erythrocytair protoporphyrine daalde met 293 μg/l. Deze veranderingen waren in de placebo groep veel minder duidelijk. Als gevolg van de ijzerbehandeling daalde de hartfrequentie gedurende het werk van 95.5 tot 91.1 slagen per minuut ($p<0.001$). Deze verlaging was omgekeerd gerelateerd aan de verandering in het hemoglobinegehalte ($r=-0.60$, $p<0.001$). De energiebesteding tijdens het werk daalde gemiddeld met 467 kJ/dag ($p<0.001$) in de met ijzer behandelde groep, terwijl in de placebogroep de daling 71 kJ/dag bedroeg ($p>0.05$). De produktie efficiëntie nam in de met ijzer behandelde groep toe met 18% ($p<0.001$). Deze toename was gerelateerd aan de stijging van het hemoglobinegehalte ($r=0.58$, $p<0.001$). Deze resultaten laten zien dat ijzersupplementering cardiovasculaire stress kan verminderen, en dat ijzersupplementering het deze vrouwen mogelijk maakte hetzelfde werk te doen met een lagere energiebesteding.

Ook het fysiek prestatievermogen voor en na ijzersupplementering werd bestudeerd. De inspanningsproeven werden gedaan met behulp van een fietsergometer. Als parameters voor het fysiek prestatievermogen werden hartfrequentiemetingen (HR), ventilatiemetingen, VO_{2max} en spierefficiëntiemetingen onder gestandaardiseerde submaximale condities verricht. Na ijzersupplementering was de hartfrequentie significant gedaald bij 4 van de 5 verschillende belastingen. De gemiddelde ventilatie was met name

lager bij de zwaardere belastingen. Een effect op de VO_{2max} kon niet worden aangetoond bij deze marginaal ijzerdeficiënte onderzoeksgroep. Maar deze populatie kan eventueel dezelfde sub-maximale belastingtesten uitvoeren op een hoger niveau van haar maximale capaciteit, wat gesuggereerd wordt door een gestegen bruto- en netto-spierefficiëntie na ijzerbehandeling. Een verbeterde arbeidsprestatie na ijzersupplementering gedurende het werk, zoals in deze studie gevonden (hoofdstuk 4), indiceert dat er mogelijk effecten zijn die niet gerelateerd zijn aan het hemoglobinegehalte. Geconcludeerd is dat marginale ijzerdeficiëntie geen invloed heeft op het maximale fysiek prestatievermogen, maar dat het wel een effect heeft op langdurige sub-maximale inspanningen.

De hier beschreven studies tonen aan dat: 1) de prevalentie van ijzergebreksanemie hoog is in vrouwelijke Chinese arbeiders in een katoenfabriek; 2) dat orale ijzersupplementering efficiënt is bij vrouwen met een slechte ijzerstatus; 3) dat het fysiek prestatievermogen, zowel gedurende het werk als ook in laboratoriumtesten verbetert met de verbetering van de ijzerstatus. Een verminderde energiebesteding gedurende het werk als gevolg van ijzersupplementering maakt het mogelijk dat de arbeidsters hetzelfde werk doen zonder onnodig vermoeid te raken. Op het einde van hun werkdag hebben zij dan nog genoeg energie voor vrijetijdsbesteding en sociale contacten; 4) dat marginale ijzerdeficiëntie waarschijnlijk geen invloed heeft op het maximale prestatievermogen, maar wel een effect op langdurige sub-maximale inspanningen.

Deze funktionele verbeteringen, samenhangend met de verbetering van de ijzerstatus, zijn van groot belang voor de sociale en economische ontwikkelingen in China. Als de ijzerstatus in vrouwen slecht is, zullen zij niet in staat zijn hun sociale rol binnen het gezin te vervullen, noch zullen zij succesvol kunnen bijdragen aan de economische ontwikkeling van hun land. Omdat het kosten/baten effect tamelijk duidelijk is, zouden er meer initiatieven tot interventieprogramma's moeten worden ontwikkeld. Het is te hopen dat niet alleen serieuze aandacht zal worden geschonken aan ernstige ijzergebreksanemie, maar ook aan ijzerdeficiëntie met marginale anemie of zelfs zonder anemie.

Curriculum Vitae

Ruowei Li was born on August 9, 1961 in Beijing, China. In 1984, after five years of studying in the Faculty of Clinical Medicine at Beijing Medical University, which was one of the ten key universities in China, she graduated with a Bachelor's Degree of Medicine. From 1984 to 1987, she was working in the Institute of Nutrition and Food Hygiene at the Chinese Academy of Preventive Medicine and was granted with a Master's Degree of Medicine. At the beginning of 1988, she arrived in the Netherlands to attend the International Course of Food Science and Nutrition (ICFSN) in Wageningen International Agricultural Centre. This course is organized in collaboration with Food and Agriculture Organization of the United Nations (FAO), World Health Organization (WHO), and United Nations Children's Fund (UNICEF). After five months , she obtained a postgraduate diploma with distinction in Food and Nutrition for Community Health and Development. Upon completion of ICFSN course, she was awarded a schlorship by the Nestlé Foundation in Switzerland, which enabled her to follow a series of training programmes with emphasis on the methodologies of energy metabolism and body composition in different countries. These included the Department of Human Nutrition at Wageningen Agricultural University (the Netherlands), the Institute of Physiology at Lausanne University (Switzerland), Dunn Nutrition Unit of Cambridge (England), and the Department of Physiology at Glasgow University (Scotland). In April, 1989, she started her research for the PhD degree in the Department of Human Nutrition, Wageningen Agricultural University under the supervision of Prof. J.G.A.J. Hautvast and Dr. P. Deurenberg. From October 1989 to November 1991, she was doing the field work for this PhD project in China. During this period, she was continually working for the Institute of Nutrition and Food Hygiene at the Chinese Academy of Preventive Medicine, and was later granted with a Doctor's Degree of Medicine. In November 1991, she came back to the Netherlands to start analyzing the data and writing the thesis up to now.

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