Attachment 1

Date: DMONO

(FACE SHEET) **ETHICAL REVIEW COMMITTEE, ICDDR,B.**

Principal Investigator: DEWAN S. ALAM

Application No. 2001-006

Title of Study: Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1)

Trainee Investigator (if any): _____

Supporting Agency (if Non-ICDDR,B) WB. NCOE

Project Status: RRC Approved

[✓] New Study

[ ] Continuation with change

[ ] No change (do not fill out rest of the form)

Circle the appropriate answer to each of the following (If Not Applicable write NA)

1. Source of Population:
   - (a) Ill subjects — Yes / No
   - (b) Non-ill subjects — (Yes) / No
   - (c) Minor or persons under guardianship — (Yes) / No

2. Does the Study Involve:
   - (a) Physical risk to the subjects — Yes / (No)
   - (b) Social risk — Yes / (No)
   - (c) Psychological risks to subjects — Yes / (No)
   - (d) Discomfort to subjects — (Yes) / No
   - (e) Invasion of privacy — Yes / (No)
   - (f) Disclosure of information damaging to subject or others — Yes / (No)

3. Does the Study Involve:
   - (a) Use of records (hospital, medical, death or other) — (Yes) / No
   - (b) Use of fetal tissue or abortus — Yes / (No)
   - (c) Use of organs or body fluids — Yes / (No)

4. Are Subjects Clearly Informed About:
   - (a) Nature and purposes of the study — (Yes) / No
   - (b) Procedures to be followed including alternatives used — (Yes) / No
   - (c) Physical risk — (Yes) / No
   - (d) Sensitive questions — (Yes) / No
   - (e) Benefits to be derived — (Yes) / No
   - (f) Right to refuse to participate or to withdraw from study — (Yes) / No
   - (g) Confidential handling of data — (Yes) / No
   - (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) / No

5. Will Signed Consent Form be Required:
   - (a) From subjects — (Yes) / No
   - (b) From parents or guardian (if subjects are minor) — (Yes) / No

6. Will precautions be taken to protect anonymity of subjects — (Yes) / No

7. Check documents being submitted herewith to Committee:
   - ___ Umbrella proposal - Initially submit an with overview (all other requirements will be submitted with individual studies
   - ✓ Protocol (Required)
   - ✓ Abstract Summary (Required)
   - ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw) (Required
   - ✓ Informed consent form for subjects
   - ✓ Informed consent form for parent or guardian
   - ✓ Procedure for maintaining confidentiality
   - ___ Questionnaire or interview schedule*

   * If the final instrument is not completed prior to review, the following information should be included in the abstract summary
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy
   2. Example of the type of specific questions to be asked in the sensitive areas
   3. An indication as to when the questionnaire will be presented to the Committee for review

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator

Trainee

ICDDR,B: Centre for Health & Population Research

RRC APPLICATION FORM

RESEARCH PROTOCOL

Protocol No.: 2001-006

FOR OFFICE USE ONLY

RRC Approval: Yes/ No Date: MAR 04, 2001

ERC Approval: Yes/No Date:

AEEC Approval: Yes/No Date:

Project Title: Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor 1 (IGF-1) in rural Bangladesh

Theme: *(Check all that apply)*

- [x] Nutrition
- [ ] Emerging and Re-emerging Infectious Diseases
- [ ] Population Dynamics
- [ ] Reproductive Health
- [ ] Vaccine evaluation
- [ ] Environmental Health
- [ ] Health Services
- [x] Child Health
- [ ] Clinical Case Management
- [ ] Social and Behavioural Sciences

Key words: Birth size, blood pressure, glucose concentration, insulin concentration, IGF-1, lipids concentration, children, Bangladesh

Principal Investigator: Dewan Shamsul ALAM Division: PHSD Phone: Ext 2209

Address: ICDDR,B, G.P.O. Box 128
Dhaka - 1000, Bangladesh

Email: dsalam@icddrb.org.

Co-Principal Investigator(s): George J. Fuchs

Co-Investigator(s): M. Yunus, M.A. Wahed, H.R. Chowdhury, Al-Fazal Khan, M. Liaquat Ali,

Student Investigator/Intern:

Collaborating Institute(s): BIRDEM, Kazi Nazrul Islam Avenue, Shahbagh, Dhaka.

Population: Inclusion of special groups (*Check all that apply*):

Gender

- [x] Male
- [x] Females

Age

- [x] 0 – 5 years
- [x] 5 – 9 years
- [x] 10 – 19 years
- [x] 20 – [illegible]
- [ ] > 65

- [ ] Pregnant Women
- [ ] Fetuses
- [ ] Prisoners
- [ ] Destitutes
- [ ] Service providers
- [ ] Cognitively Impaired
- [ ] CSW
- [ ] Others (specify _____)
- [ ] Animal

Project / study Site (*Check all the apply*):

- [ ] Dhaka Hospital
- [ ] Matlab Hospital
- [x] Matlab DSS area
- [ ] Matlab non-DSS area
- [ ] Mirzapur
- [ ] Dhaka Community
  - Chakaria
  - Abhoynagar
- [ ] Mirsarai
- [ ] Patyia
- [ ] Other areas in Bangladesh _____
- [ ] Outside Bangladesh
  - name of country: _____
- [ ] Multi centre trial
  - (Name other countries involved)

Revised on: 30 May 2000

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☑ Secondary Data Analysis
- ☐ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☑ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☑ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- ☐ Others

Targeted Population *(Check all that apply)*:

- ☑ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal groups
- ☐ Expatriates
- ☐ Immigrants
- ☐ Refugee

Consent Process *(Check all that apply)*:

- ☑ Written
- ☐ Oral
- ☐ None
- ☑ Bengali language
- ☑ English language

Proposed Sample size:

Total sample size: ~ 400 ☐

Sub-group Normal birth weight ~ 200 ☐ Low birth weight ~ 200 ☐

_____ ☐ _____ ☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

- ☐ Human exposure to radioactive agents?
- ☐ Fetal tissue or abortus?
- ☐ Investigational new device? (specify_____)
- ☐ Existing data available from Co-investigator
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug
- ☐ Existing data available via public archives/source
- ☐ Pathological or diagnostic clinical specimen only
- ☐ Observation of public behaviour
- ☐ New treatment regime

Yes/No

☑ ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

Ar

☐ ☑ Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduc such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☑ a. place the subject at risk of criminal or civil liability?

☐ ☑ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc

Do you consider this research *(Check one)*:

- ☐ greater than minimal risk
- ☐ no risk
- ☑ no more than minimal risk
- ☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☑ ☐ Is the proposal funded?

If yes, sponsor Name: World Bank through NCOE 3rd yr Grant.

Yes/No

☐ ☑ Is the proposal being submitted for funding ?

If yes, name of funding agency (1) _____

(2) _____

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support

(Day, Month, Year - DD/MM/YY)

Beginning date ASAP

End date 10 month from date of start!

Cost Required for the Budget Period ($)

a.	*1st Year*	*2nd Year*	*3rd Year*	*Other years*
	86,013			

b. *Direct Cost:* 74,794 *Total Cost:* 86,013

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Prof. Lars Åke Persson — Name of the Division Director

✓ Signature

11/2/2001 — Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI

Date: 10 Feb 2001

Name of Contact Person (if applicable)

P.I.

Table of Contents

PROJECT SUMMARY

Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely th experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise an accurate description of the proposed research is required. This summary must be understandable and interpretable when remove from the main application. (TYPE TEXT WITHIN THE SPACE PROVIDED).

Principal Investigator: Dewan Shamsul Alam

Project Name: *Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1) in rural Bangladesh*

Total Budget: US$ 82,286 Beginning Date ASAP Ending Date: 10 months from the date of Start

Coronary heart disease (CHD), hypertension, and non-insulin dependent diabetes are leading causes of morbidity and mortality among adult population. The prevalence of these diseases has increased in developing countries, and it is believed that developing countries will face an epidemic of these diseases in near future. Following the initial report of Barker, additional evidence has accumulated to suggest that such diseases are disproportionately higher among those who were born smaller in size. It is thought that nutritional insult during a critical period of fetal life has permanent effects on wide range of structural, metabolic and physiologic functions. Therefore, low birth weight infants who survive through infancy and childhood are likely to be at greater risk for chronic diseases in later life. Experimental studies in animals, and human epidemiologic studies provide strong evidence to support the "Bareker's hypothesis" which is now commonly known as "fetal programming" for adult disease.

It is estimated that 20% of infants are low birth weight (LBW) globally, with Bangladesh having the highest rates of (50%) in the world. This high prevalence of LBW in Bangladesh is mainly attributable to intrauterine growth retardation resulting from maternal undernutrition. Because these LBW infants supposedly experienced intrauterine nutritional insult, they are believed to be at increased risk for coronary heart disease, hypertension, stroke, non-insulin dependent diabetes, and other metabolic abnormalities in later life. Recent studies have shown that higher blood pressure and some metabolic abnormalities are present among lower birth weight categories during their childhood as early as 4-8 years of age. However, most evidence is from developed countries where birth weight is relatively higher and low birth weight, especially IUGR rate is much lower. Therefore, it is also important to determine whether physiologic, metabolic and hormonal profile in low birth weight predictive of future risk for chronic disease are also prevalent in our population.

We propose a cross-sectional study design to examine the relationship between weight at birth and childhood blood pressure, fasting glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1). This study will be conducted in a cohort of approximately 400 children (currently aged 5-6 yrs) who participated along with their mothers in our previous study (1995-7) in which birth weight and other parameters of size at birth were meticulously collected. The mean birth weight was 2.51 kg and 48% were born low birth weight. Also growth during the first 6 month of infancy, dietary intakes and morbidity data were collected. In the current study, the children's nutritional status, dietary intakes, blood pressure, lipid profile, fasting blood glucose, plasma insulin and (IGF-1) will be measured. Information on socioeconomic and household characteristics, as well as parental factors will also be collected to control for possible confounding variables.

Data will be analyzed to examine the relationship between different parameters of size at birth and the outcome variables. Results of the univariate analyses will be further examined in appropriate multivariate model (multiple linear regression/multiple logistic regression) to adjust for possible confounding and also to identify possible interactions between variables.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	Professional Discipline/ Specialty	Role in the Project
1. Dewan Shamsul Alam	Medical doctor specialized in Human Nutrition and Epidemiology	Principal Investigator
2. Md Yunus	Senior Scientist and Head MHRP, PHSD	Co-Investigator
3. M.A. Wahed	Head Nutrition Biochemistry Laboratory	Co-Investigator
4. H.R. Chowdhury	Physcician-In-Charge, CRU, MHRP	Co-Investigator
5. Al-Fazal Khan	Medical Officer, CRU, MHRP	Co-Investigator
6. Md. Liaquat Ali	Biochemist and Scientist, BIRDEM, Dhaka	Co-Investigator
7. George J. Fuchs	Associate Director, CSD	Co-Investigator

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

1. The mean blood pressure (systolic and diastolic) and therefore the risk for hypertension is higher among children born low birth weight (LBW) compared to their normal birth weight counterparts.
2. Fasting blood glucose concentration and plasma insulin concentration and therefore the risk for NIDDM is higher in children born LBW compared to their normal birth weight counterparts.
3. Elevated/Dyslipidaemia (lipid abnormalities) is more prevalent among children who were born LBW than those who were born with normal birth weight.
4. Plasma insulin-like growth factor 1 (IGF-1) concentration will be greater in children who were born low birth weight than their normal birth weight counterparts.

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods (TYPE WITHIN LIMITS).

1. To compare the mean blood pressure between children who were born LBW and those who were born normal birth weight.
2. To compare fasting blood glucose concentration between children who were LBW and those who were born normal birth weight.
3. To compare fasting plasma insulin concentration between LBW and normal birth weight groups.
4. To compare the lipid profile between children who were LBW and that of those who were normal birth weight.
5. To compare insulin-like growth factor-1 (IGF-1) concentration between children who were LBW and that of those who were normal birth weight.

Principal Investigator: Dewan Shamsul Alam

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. **(DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).**

Birth weight has been shown to be a significant predictor of mortality, morbidity and survival during infancy and childhood (McCormick 1985). Low birth weight infants are especially at greater risks for these adverse outcomes; and child survival data from developing countries are consistent with that (UNICEF 2000). The overall global prevalence of low birth weight is reported to be 20% of all births. However, the prevalence is disproportionately higher in South Asian countries particularly in Bangladesh, India and Pakistan as compared to the global prevalence. The scenario is the worst in Bangladesh where 50% of all births are reportedly low birth weight, which means that out of an estimated 3.3 million annual births; over 1.5 million are born with low birth weight (UNICEF 2000). This high rate of LBW South Asian countries is mainly attributable to intrauterine growth retardation resulting from undernutrition during fetal life (de Onis, Villar, & Gülmezoglu 1998;Villar & Belizan 1982).

Recent reports suggest that those who suffer undernutrition in utero and born small, remain disadvantaged throughout their lifetime due to possible persistent effect of undernutrition during fetal life on wide range of metabolic, physiologic and structural parameters (Barker 1995a;Fall et al. 1995a;McKeigue et al. 1993;Whincup et al. 1999). It is thought that nutritional insult during a critical period of fetal life 'programme' such outcomes. Experimental studies with animals (Woodall et al. 1996), and most human epidemiologic studies in developed and developing countries have consistently shown that those who are small at birth are known to have increased rates of coronary heart disease (Barker 1995b;Barker & Osmond 1986), hypertension (Law & Shiell 1996), and non-insulin dependent diabetes (Lithell et al. 1996;McKeigue et al. 1988) in adult life. Therefore, low birth weight infants who survive through infancy and childhood are likely be be at greater risks for coronary heart disease, hypertension and non-insulin dependent diabetes in later life.

Prevalence of CHD, hypertension, and diabetes

Chronic diseases such as hypertension, diabetes and coronary heart diseases are leading causes of morbidity and mortality among adult populations in both developed and developing countries. However, the prevalence of these chronic diseases are disproportionately higher, and in the rise in many developing countries, and it is believed that developing countries are in the verge of chronic disease epidemic (World Health Organization 1997). South Asian populations, at home and also those who are settled in developed countries, are known to have greater risk for mortality and morbidity due to coronary heart disease (CHD). Preponderance of CHD and its risk factors among South Asian populations has been linked to their poor circumstances during fetal life which might have caused "programming" for later life (Barker 1995a).

CHD accounts for an estimated 14% of total deaths or over 7.4 million deaths globally, majority of those occur in developing countries (World Health Organization 1997). While CHD deaths are declining in most Western industrialized countries, there is an increasing trend in developing countries. Although population based data on cardiovarcular disease are not available for Bangladesh, observations in the hospitals indicate a high prevalence, and notably incidence of the disease at relatively younger age than in Western populations.

Hypertension is one of the major risk factors for coronary heart disease and is prevalent among 20% of adult population globally. It is reported that 10% of rural population over 15 years of age suffer from hypertension (Sayeed et al. 1995). Another report based on pooled analysis of data from several prevalence study of hypertension showed that over 11% of adults in Bangladesh suffer from hypertension (Zaman & Rouf 1999).

Non-insulin dependent diabetes and impaired glucose tolerance are increasingly becoming more common among adult populations in developing countries than in developed countries (World Health Organization 1997). It is reported that the prevalence of non-insulin dependent diabetes among 30-60 year is between 3-10% in European, in contrast, the prevalence among migrant Asian population is reported to be 14-20% (King & Rewers 1993). A recent survey in Bangladesh showed 8% of urban and 4% of rural population aged 30-64 years suffer from NIDDM and 17% of rural population have impaired glucose tolerance (Sayeed et al. 1997).

It is believed that developing countries are on the verge of facing epidemic of chronic diseases particularly of coronary heart disease, hypertension and non-insulin dependent diabetes. According to WHO, this trend is mainly attributable to aging of

population, unhealthy habits and behavior, and bad dietary practice (World Health Organization 1997). However, populations in developing countries are also disadvantaged during their fetal life and early postnatal periods as evident by high prevalence of low birth weight and poor postnatal growth. Ample of available data suggest that nutritional insult during those critical periods have permanent effect on metabolic and physiologic functions which increases their susceptibility to chronic diseases in later life. This aspect has not been yet considered in the etiology of chronic diseases in developing countries.

Epidemiologic evidence of association between size at birth and chronic diseases

Size at birth and coronary heart disease

The association between size at birth and mortality and morbidity due to coronary heart disease has been reported in several studies. Initial observations that lead to investigation into the association between size at birth and coronary heart disease came from ecological studies that showed association between place of birth and risk for CHD (Barker & Osmond 1986;Forsdahl 1977). It was thought that the circumstances that lead to perinatal mortality also associated with increased risk for cardiovascular disease in later life (Ben-Sholomo & Smith 1991). Several retrospective studies based on large cohorts looked at the association between size at birth and CHD mortality in adults. In a study in Hertforshire, UK, both birth weight and weight at 1 hear were inversely related to cardiovascular mortality, although the association between weight at 1 year and CHD mortality was not adjusted for birth weight (Osmond et al. 1993). In Sheffield, England, CHD mortality in a cohort was inversely related to both birth weight and ponderal index (Barker 1992). Mortality due to CHD among male and female adult populations of South Asian origin settled in overseas has been reported to be higher than other ethnic groups (McKeigue, Miller, & Marmot 1989). Although size at birth data were not available for those who had their origin in South Asia, they were supposedly had lower birth weight than those of the other ethnic group. Another study in India reported an inverse relationship of CHD mortality with birth weight and socioeconomic status (Stein et al. 1996). However, the effect of birth weight was not significant after adjusting for SES.

Morbidity due to CHD has been shown to be associated with size at birth and growth during early life. One study in Sheffield, England showed that CHD morbidity was significantly related to weight at 1 year but not with birth weight (Fall et al. 1995b). However, most retrospective studies are criticized for lack adjustments for the possible confounding variables particularly body mass index (BMI) for its established relationship with birth weight and also with the outcome. Franknel et al. (Frankel et al. 1996) showed that risks for cardiovascular disease in adult men (45-59 years) was inversely related with birth weight. Adjustment for BMI did not change the association between birth weight and cardiovascular disease (CVD) risks. Birth weight has also been shown to be inversely related non-fatal cardiovascular disease (myocardial infarction or stroke) in Nurses' Health Study in the USA (Rich-Edwards et al. 1997). The strength of association remained unaffected after controlling for childhood socioeconomic status and adult lifestyle variables. A more recent study in Helsinki, Finland showed a graded decrease in hazard ratio for CHD among adults women with the increase in birth weight and birth length (Forsen et al. 1999). However, whose who were short at birth and attained highest height at 7 years of age had the greatest hazard ratio for CHD. This indicates that some postnatal growth factor is also involved in increasing the risk for CHD. Populations of South Asian origin generally have lower birth weight than those of European origin. Another recent study in men and women in UK reported higher prevalence of impaired glucose tolerance (IGT), diabetes, low high density lipoprotein cholesterol (HDL-C), high triglycerides (TG), and evidence of myocardial infarction among South Asian than European origin (Bhopal et al. 1999). However, prevalence of hypertension in South Asian men was lower than European. In conclusion, retrospective studies, despite inherent limitations, consistently support an inverse relationship between birth weight and coronoary heart disease mortality and morbidity. However, further study need to be carried out to explain the mechanisms that causes higher propensity of CHD among low birth weight.

Size at birth and blood pressure

Numerous studies support the inverse relationship between birth weight and blood pressure in later life. A study with English men who were identified from hospital record showed that systolic blood pressure (SBP) was inversely related to birth weight and directly to placental weight (Barker et al. 1990). Study in 10-12 year old children in Jamaica showed a negative association between maternal nutrition during pregnancy and children's blood pressure (Godfrey et al. 1994). An experimental study with rats randomized to *ad libitum* or 30% *ad libitum* intake followed for their growth and blood pressure showed that the offspring of the food-restricted group had significantly higher systolic blood pressure at 30, 48, and 56 week of age (Woodall, Johnston, Breier, & Gluckman 1996). These results indicate that undernutrition during fetal life may have some permanent effect on cardiovascular homeostasis. Another study in Swedish men reported a similar inverse association between birth weight and SBP and the association was strongest among for those who were in the upper tertile of BMI (Leon et al. 1996). They also showed that those who were light at birth but grew taller had the greatest risk for hypertension. Their findings indicate potential interaction between birth weight and later growth. Recent review of literature on blood pressure and birth weight in both adults and children has supported the inverse association (Law & Shiell 1996). However, a large study in Israelly adolescent, 6684 men and 4199 women born between 1974 and '76, observed no association between maternal nutrition or IUGR, and SBP (Laor et al. 1997). An earlier study in Israel showed a small but a positive correlation between birth weight and SBP at 17 years (Seidman et al. 1991). Recent results from The Avon Longitudinal Study of Pregnancy and Chilldhood (ALSPAC) in England which examined the association between birth weight and blood pressure in 1,860 children at 3 years of age showed that birth weight had an inverse relationship

with both systolic and diastolic blood pressure after controlling for height and body mass index (Whincup, Bredow, Payne, Sadler, Golding, & the ALSPAC Study Team 1999). While the authors did not rule out the possibility of "programming", they concluded that lack of independent relationship of other measures of size at birth such as length, head circumference and ponderal index provide no support to specific period of fetal growth as central importance. In conclusion, evidence from different studies are consistent with regard to inverse relationship between birth weight and blood pressure. It is yet unclear whether the inverse relation between birth weight and blood pressure amplify with increasing age and what are the factors that can be targeted for modification.

Glucose and insulin concentrations, and insulin resistance

Smaller size at birth has been consistently shown in several studies to be associated with, higher fasting glucose concentration, impaired glucose tolerance, and development of non-insulin dependent diabetes mellitus in adult life (Barker 1992;Phillips et al. 1994). Increased plasma insulin concentration and insulin resistance in adults who had low birth weight have been reported in several studies (Barker 1992;Hales et al. 1991). Although the mechanism is not yet clear, it is postulated that undernutrition during fetal life may cause muscle to become resistant to insulin sparing the brain, and this insulin resistance persists in later life. Retrospective studies in England reported several times higher rate of IGT and non-insulin dependent diabetes mellitus among those who had birth weight ≤ 2.5 kg or lower ponderal index (Wt_{kg}/Ht_m^3)(Hales, Barker, Clark, Cox, Fall, & Osmond 1991;Phipps et al. 1993). A study in Swedish men aged between 50-69 years reported an inverse relationship between birth weight and fasting insulin and blood glucose concentration, and adjustment for BMI did not affect the strength of association (Lithell, McKeigue, Berglund, Mohsen, Lithell, & Leon 1996). An inverse association between ponderal index and fasting insulin concentration has been reported in Mexican women (Valdez et al. 1994).

While studies with adults are criticized for their long gap between exposure and outcome and poor control of important confounding variables, studies with children are less vulnerable to such criticisms. Evidence of inverse association between size at birth and insulin resistance is available from studies with children also. Studies in both developed and developing countries have shown evidence of reduced insulin sensitivity among children who were born low birth weight or had low ponderal index. A study in 4 year old children in India who had low birth weight showed higher glucose and insulin concentration 30 min after an oral glucose load (Law et al. 1995). A similar study in Salisbury, England in 7 year old children who had low ponderal index (Wt_{kg}/Ht_m^3) at birth showed evidence of reduced insulin sensitivity (Yajnik et al. 1995). A recent follow-up study of Indian cohort at 8 years revealed that the highest level of insulin resistance variables were observed in children of low birth weight but had high fat mass at 8 years (Bavdekar et al. 1999). However, most insulin-resistant children were the taller ones who had short mothers. In conclusion, studies in both adults and children showed strong evidence of insulin resistance supporting the hypothesis that insulin resistance might have developed during fetal life as a result of undernutrition that persists on to later life.

Birth weight and dyslipidemia

Although population of South Asian origin settled in Western countries have lower serum total cholesterol, they have low plasma high density lipoprotein and high triglyceride concentrations. It is known that low HDL-C and high TG are both potential risk factors for coronary heart disease. Study in East London showed that Bangladeshi men and women had lower serum HDL-C and lower HDL/TC ratio than other ethnic groups (McKeigue, Miller, & Marmot 1989). Both low HDL-C and low HDL/TC ratio are risk factors for CHD. Another study in the U.S. reported that Indian settlers had lower HDL-C and higher TG than general population suggesting an increased risk for CHD among Indian origin. Since South Asian populations are generally known to have lower birth weight than Western populations, it might be possible that dyslipidemia is associated with their small size at birth was also programmed during fetal life.

Birth weight and IGF-1

Low birth weight is known to be associated with persistent changes in secretion of and sensitivity to hormones that regulate fetal growth including insulin and insulin-like growth factor-1 (IGF-1). Changes in concentrations and of sensitivity to these hormones are believed to be one of the mechanisms causing increased rates of cardiovascular disease among low birth weight (Barker 1995b;Osmond, Barker, Winter, & Fall 1993). The mitogenic action of growth hormone is mediated through IGF-1. Biochemically insulin and IGF-1 one are closely related and both, although by different mechanism, are involved in pre- and postnatal growth. Recent study reported a higher circulating concentration of IGF-1 among children who had lower birth weight than their heavier counterparts (Fall, Pandit, Law, Yajnik, Clark, Breier, Osmond, Shiell, Gluckman, & Barker 1995a). The results were consistent across children in developed and developing countries (England and India respectively). The negative association of IGF-1 with birth weight persisted after controlling for the current body size. Also a positive association between IGF-1 and systolic blood pressure was observed in that study. Hypertension is one of the major risk factor for coronary heart disease (World Health Organization 1997). It is speculated that IGF-1 might also be involved in the process of increasing risk for coronary heart disease in low birth weight.

Principal Investigator: Dewan Shamsul Alam

Rationale and Significance of the Study

It is established that birth weight is a strong determinant of mortality, morbidity and growth during infancy and childhood. Nearly 50% of all births are low birth weight in Bangladesh, and most of these LBWs are due intrauterine growth retardation resulting from undernutrition during fetal life. There is now evidence that fetal undernutrition is associated with permanent effects on important structural, metabolic and physiologic parameters which predispose lower birth weight infants to hypertension, diabetes and coronary heart disease in adults. Therefore, this extremely high prevalence of LBW in our country is a compelling reason to investigate this issue and put strategies in place to prevent long-term consequences.

Low birth weight, one of the major public health problem in Bangladesh, has already received priority in national nutrition intervention program because of its consequences with regard to survival and growth during infancy and childhood. If low birth weight is found to be associated with hypertension and metabolic abnormalities predictive of risk for chronic diseases (particularly diabetes and coronary heart disease), it will further emphasize the importance of intervention for low birth weight and improvement of maternal nutrition.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

Study site and population

The study will be conducted in the 16 villages in Matlab Upazila under Chandpur district in Balgadesh where our previous study "Dietary fat and infection: effect on vitamin A status of mother and infant and dietary intake methodology" was implemented between October 1995 and November 1997. In that study a total of 676 pregnant women were recruited of which 340 were from eight intervention villages and other 336 from the control villages. Women in the intervention villages received 20 ml soybean oil daily as supplement from enrollment up to six month postpartum while the women from the control villages received no supplement. In total 326 intervention women and 315 control delivered singleton babies. Eighty percent of there infants were measured within 72 hours after birth. There was no difference in birthweight or other measurements (length, chest and head circumference) of size at birth between infants of intervention and control mothers. About 48% were born with low birth weight (<2500 g). Those who were measured within 72 hours after birth and currently resident in the study villages will be invited to participate into the current study. As the population is fairly stable, only a very few children are expected to have migrated out of the study area. Availability of the children will be initially checked in records of Matlab Health and Demographic Surveillance System, which maintains regularly updated demographic data on all population (~220,000) in Matlab ICDDR,B study area which covers nearly a half of Matlab Thana that include all previous study villages (van Ginneken et al. 1998). A door-to-door survey will also be conducted to confirm the availability of the children.

Study Design

A cross sectional study design will be used to evaluate the study hypotheses. Major grouping will be considered based on birth weight (Low/Normal birth weight) although other major parameters of size at birth such as length and ponderal index will also be considered. From the available list of children required number of children from each group (LBW/NBW) will be randomly selected for the study. After obtaining a written informed consent, children and their mothers will be recruited in the study. Blood pressure, fasting blood glucose, lipid profile, fasting plasma insulin concentration, IGF-1, current body size, and dietary intakes will be measured. Also data on socioeconomic status and parental factors will be collected. Trained workers will take all the measurements in the clinic at Matlab.

Anthropometric measurements

Data on size at birth will be available from our previous study. In that study birth weight was measured within 72 hours with SECA beam balance accurate to 10g. Birth length was measured to the nearest 0.1 cm with locally constructed wooden length board. Length was measured twice and the mean was recorded as the birth length. For the current study weight, height and mid upper arm circumference will be measured following standard guidelines (Gibson 1990). Workers will be trained on anthropometric measurements of children and go through WHO suggested anthropometric standardization procedures (Measuring Change). Weight will be measured with portable SECA electronic scale to nearest 100 g. Height will be measured to nearest 0.1 cm with Accu-Hite Stadiometer with built in leveling bubble.

Dietary Assessment

Children's dietary intakes will be assessed by 24-hour dietary recall method. Trained interviewers will conduct dietary interviews with mothers to report what their children ate during the last 24 hours. Standard guidelines will be followed during interview (Gibson 1990). Standardized household measures (cups, utensils, etc.) will be used to estimate the quantity of each food. Nutrient intake will be calculated from food intake data using computerized food composition table appropriate for Bangladeshi foods which was developed using nutrient data from regional food composition databases ((Helen Keller International (HKI) 1988;National Institute of Nutrition 1989). Dietary data will be collected to characterize group intake. We are not aiming to relate dietary factors directly to any of the outcomes, but are interested in controlling for dietary intake, especially fat intake.

Blood pressure
Trained worker will measure the blood pressure twice in the left arm using a DINAMAP blood pressure monitor (Critikon Inc., Tampa, Florida) after the child had rested at least 5 minutes or when at sleep. This device is free from observer influence and has high reliability. The average of the two measurements will be recorded as the child's blood pressure. The average of two measurements will provide a representative blood pressure for the subject. Both systolic and diastolic blood pressure will be measured. Single appropriate child cuff will be used in all children. The instrument will be calibrated daily or according to the manufacturer's instruction. All blood pressure measurements will be taken when the child is calm. There is no strict definition of childhood hypertension as for the adult hypertension. Therefore, children will be classified as "normal" if their blood pressure fall below 90th percentile, "high normal" if their blood pressure fall between 90th and 95th percentiles and as "hypertensive" if >95th percentile for age- and sex-adjusted values (Rosner et al. 1993) .

Plasma lipids concentration
Blood specimen (5 ml) will be collected by antecubital venipuncture. Study physician or trained and experienced nurse will draw the blood specimen following aseptic procedure. Anaesthetic cream or spray will be used at the venepuncture site to minimize pain. All mothers or caretakers will be instructed to have their infants fast with the exception of water for at least 8 hours before the blood specimen is collected. Fasting total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), will be determined by enzymatic colorimetric method using Randox kit of UK. Trigyceride (TG) will be determined by enzymatic colorimetric method using kit from Human GmbH of Germany. Low-density lipoprotein cholesterol (LDL-C) will be calculated by using the Friedewald formula (Friedewald, Levy, & Fredrickson 1972). Abnormal lipid and lipoprotein values will be defined as greater TC, LDL-C, TG or lower HDL-C than their age- and sex-adjusted 95th percentile value (National Istitute of Health 1979). Children will be classified based on lipid values as "elevated LDL-C", "isolated TG/HDL-C", "borderline" and "normal"(Polonsky, Bellet, & Sprecher 1993).

Blood glucose, insulin, and IGF-1 concentration
Blood glucose will be determined by enzymatic (glucose oxidase) colorimetric method in automated Opera Chemistry Analyzer of Bayer Diagnostics using kit from Boehringer, Germany or Randox, UK. Fasting plasma insulin concentration will be measured by particle-enhanced fluorescent ELISA method (Abbott, USA). Insulin like growth factor 1 (IGF-1) will be determined by enzyme immunoassay (DRG, Germany). Blood sample for insulin and IGF-1 will be collected in container containing aproteinin (Tracilol, Sigma Aldrich) to prevent possible breakdown of protein during storage (5-7 days in –20 °C) before analysis.

Parental factors
Maternal height, educational level, socioeconomic status will be used from earlier study. In addition, history as well as the current status with regard to hypertension, diabetes, CHD (using Rose/WHO questionnaire) will be ascertained.

Quality of data
Using pretested validated questionnaires data quality will be ensured. Workers will be properly trained before data collection. Refresher training will be arranged during the study period to enhance further quality of data collection. Weighing scales will be calibrated daily before use. Experienced workers under supervisor of senior staff will take anthropometric measurements in the clinic. All data forms will be examined manually for consistency before entry to the computer. Also measures will be taken in data entry program to check inconsistency and error.

Estimation of Sample size

Sample size was calculated for key outcome variables to detect important differences differences at 5% significance level with a power of 80% (Table 1.). We consider a 10% possible refusals or withdrawal of subjects after initial consent. Calculations of sample size for testing differences in blood pressure have been found to be adequate for testing other hypotheses related to other outcome variables given their respective inherent variations. Although we calculated the sample size requirements based on only two categories low birth weight (LBW and normal birth weight (NBW) we planned to include all available children who were born singleton and had their birth weight measured within 72 hours to have greater power to do subgroup analysis. Most of the study demonstrated relationship between size at birth and later outcome had very low LBW rates.

Principal Investigator: Dewan Shamsul Alam

Table 1. Sample size estimates for various outcome variables.

Comparison groups	Outcome	Minimum detectable difference	SD	No. of subjects per group	Total sample	No. of subjects expected to be available	Reference (age group studied)
LBW vs NBW	Systolic B.P. (mm Hg)	2 mm Hg	7	192	422	420	Whincup et al. 1999 (~3 y)
LBW vs NBW	Diastolic B.P. (mm Hg)	2 mm Hg	6.5	166	360		
LBW vs NBW	IGF-1 (ng/ml)	7	23	170	374		Fall et al. 1995 (~4 y Indian, 7-9 y England)
<2.00 kg vs >=2.00 kg	Fasting glucose (mmol/L	0.3	0.6	63	140		Bavdekar et al. 1999 (~8 y)
LBW vs NBW	Fasting insulin (pmol/L)	5	12.5	98	216		
LBW vs NBW	LDL (mmol/L	0.2	0.6	141	310		

Principal Investigator: Dewan Shamsul Alam

Timetable

Activity	Month									
	1	2	3	4	5	6	7	8	9	10
Preparatory activities	X	X								
Recruitment and training		X	X							
Survey and data collection		X	X	X	X	X				
Laboratory analysis			X	X	X	X	X			
Data entry and cleaning				X	X	X	X	X		
Data analysis						X	X	X		
Reporting							X	X	X	X

Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. (TYPE WITHIN THE PROVIDED SPACE).

The proposed study will be implemented in Matlab field research area of International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). The Centre has maintained a free diarrhoea treatment hospital in Matalb. ICDDR,B's Health and Demographic Surveillance System (HDSS) in Matlab has been regularly updating demographic information on 220,000 population (currently) in 72 villages since 1963. The study children and their mothers are the permanent residents in 16 villages in Matlab study area of ICDDR,B and participated in our previous study. Their current residence status can be easily identified through records available from Matlab HDSS. The clinic facilities available in Matlab will be used for this study. ICDDR,B transport facilities (speedboats/country boats) will be used for field visits and transportation of mothers and children. All data collection including blood specimens will be completed in the clinic ensuring all possible safety measures. The storage facilities (freezers –20 C) available in Matlab laboratory will be used for temporary storage of samples before they will be transported to Dhaka for analysis. ICDDR,B has excellent laboratory facility in Dhaka where blood glucose concentration and lipid profile will be measured. Plasma fasting insulin and IGF-1 concentrations will be measured in the biochemistry laboratory in BIRDEM (collaborating institute).

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. (TYPE WITHIN THE PROVIDED SPACE).

Data will be examined and analyzed using statistical software SPSS-PC for Windows. All variables will be examined for their distributions, and necessary transformations of the non-normally distributed variables will be made if required for normalizing their distribution and statistical tests. Data will be presented as mean and standard deviation for the normally distributed variables and as frequencies and percentages in case of categorical variables. Continuous variable will be compared by Student's t-test or one way analysis of variance followed by appropriate multivariate analysis to adjust for the possible confounding variables and to examine for the interactions. Regression analysis will also be performed to examine the change in outcome variable with unit change in size at birth. Categorical variables will be compared by chi-square tests. In case of binary outcome variables, multiple logistic regression will be done to identify significant independent variables while controlling for the effect of the confounding variables. Analyses will be focused on assessing the association between various parameters of size at birth (weight, length, body proportionality). Also interactions with maternal height and weight will be examined using appropriate statistical models.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

Children and their mothers will be enrolled in the study after obtaining informed written consent from the mother. Both mother and child may withdraw from the study without any obligation and without affecting their access to ICDDR,B and government health services in Matlab. Any study participant with health problem will be given immediate treatment and advice. Confidentiality of information provided by the study participants will be strictly maintained. Ethical approval for this study will be sought from the institutional review committee at ICDDR,B.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

No animal will be used in this study.

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

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Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

Initial results will be disseminated through short reports and working papers. Major results and conclusions will be disseminated through working papers, journal articles and presentations at national, regional and international conferences and meetings.

Principal Investigator: Dewan Shamsul Alam

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. (DO NOT EXCEED ONE PAGE)

This study involves collaboration with Bangladesh Institute Of Rehabilitation Of Diabetic Endocrine And Metabolic Disorders (BIRDEM). A memorandum of understanding with BIRDEM is in advanced stage of preparation. The main area of collaboration would to assist in establishing assays for insulin and insulin like growth factor-1 (IGF-1) and the interpretation of biochemical results. We have also established contact with Division of Human Nutrition & Epidemiology, Wageningen University, the Netherlands. The main area for collaboration with Wageningen University would be in the field of dietary assessments and software support for dietary data analysis.

APPENDIX

International Centre for Diarrhoeal Disease Research, Bangladesh

Voluntary Consent Form

Title of the Research Project: *Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1) in rural Bangladesh.*

Principal Investigator: Dewan Shamsul Alam

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

Birth weight of infants in Bangladesh is generally lower than other populations in the world. In Bangldesh about 50% of the infants are born with low birth weight (<2500 g at birth). This low birth weight or small size at birth of Bangladeshi infants is considered to be an outcome of undernutrition during fetal life. Studies have shown that there is strong association between size at birth and later development of diabetes, hypertension and coronary heart disease in adult life that is believed to occurs as consequences permanent changes in physiologic and metabolic functions in response to fetal adaptation to undernutrition. Although these disease conditions are rare during younger age groups, some metabolic physiologic changes that occur in response to fetal undernutrition are detectable during childhood. Since infants in our country born with relatively lower birth weight they are likely to have greater risks for those abnormal metabolic conditions. ICDDR,B has planned to conduct a study to investigate whether children in rural Matlab have any abnormal blood pressure or metabolic or hormonal functions.

In this study you and your child are invited to participate. Your participation will be completely voluntary and only once during the study period. If you allow your child to participate into this study, s/he will be required to allow us to measure his current body size, blood pressure, dietary intakes. S/he will also be required to provide 5 ml or one teaspoon equivalent of venous blood from his/her antecubital vein to examine whether his/her blood glucose and other metabolic indicators are normal or abnormal. Doctor or a trained nurse will collect blood very carefully using sterile and disposable syringe and needles. We will take necessary precaution so that blood collection is safe and cause minimum possible pain to your child. Although the possibility is very rare, in some cases extravasations blood may occur even after adequate precaution and technique. If it happens to your child we shall immediately take appropriate measure and provide adequate treatment if necessary.

There is virtually no risk for you and your child if you participate into this study. If your child has any abnormal condition detected through our investigation, you will be informed and the professional staff will provide necessary advice. Your participation is absolutely voluntary. You may ask any questions regarding the study and we shall be happy answer them for you. You have the right to withdraw from the study any time even after giving a written informed consent without jeopardizing you and your child's routine services that are provided by ICDDR,B. If you or your child feel sick during the study we shall provide you necessary treatment and advice. We assure you that the identity of your child will remain confidential in any publication or dissemination resulting from this study.

Principal Investigator: Dewan Shamsul Alam

We now invite you and your child to participate in the study. If you agree to participate please sign or provide your left thumb impression on the consent document.

Consent: The study has been clearly explained to me, and I voluntarily consent for my child and myself to participate in it. I, having full capacity to consent do hereby give consent for me and my child to participate in this study._____;

RID_____, CID _____, age _____

Signature/LTI of mother _____ Date _____

Name of witness _____ Signature of witness _____

Signature of Investigator _____ Date _____

_____ _____

Signature of Investigator/ or agents

Date:

Signature of Subject/ Guardian

Date:

Continuation Sheet (Number each sheet consecutively)

D.S. Alam et al.

Budget

	Rate (US$)	Effort (Person-months)	Amount US$
Professinal Scienctific Staff			
Dewan S. Alam (PI)	1163/mo	30% (3)	3,489
George J. Fuchs (Co-PI)		5% (.5)	-
M. Yunus (Co-Investigator)	2220/mo	10%(1)	2,220
M. A. Wahed (Co-Investigator)	1478/mo	5% (0.5)	739
H. R. Chowdhury	1163/mo	5% (0.5)	581
Al-Fazal Khan (Co-Investigator)	587/mo	20% (2)	1,174
Liaquat Ali (Co-Investigator)		10% (1)	-
Subtotal			**8,203**
Field Staff			
Study Medical Officer NOA (1)	659/mo	100% (5)	3,295
Study Nurse GS5 (1)	351/mo	100% (5)	1,755
Senior Field Research Assistant GS4 (1)	250/mo	100% (5)	1,250
Field Research Asst G3 (4)	225/mo	100% (20)*	4,500
Laboratory Assistant G3 (1)	225/mo	100%(5)	1,125
Office/Data management assistants G3 (1)	225/mo	100% (6)	1,350
Community Health and Research Worker GS1 (12	168/mo	50%(30)**	5,040
Rickshaw puller/Baotman (4)	60/mo	100% (20)***	1,200
Subtotal			**19,515**
Equipments			
Dinamap blood pressure monitor and cuff (2)			2,200
Electronic Weighing Scales (2)			2,500
Stadiometer (2)			600
Computer (1)			1,800
Printer (1)			1,200
Freeze (1)			700
Subtotal			**9,000**
Supplies and Materials			
Blood collection/storage tubes (microtainer/cryovials)			1,500
Medicine			1,200
Office furniture			600
Office and other supplies			1,200
Subtotal			**4,500**
Biochemical tests			
Blood glucose	2	420	840
Fasting plasma insulin concentration	12	420	5,040
Plasma lipid profile (TC, HDL-C, TG)	13	420	5,460
IGF-1	14	420	5,880
Subtotal			**17,220**
Travel			
Local (Dhaka - Matlab)			1,500
Fuel and transportation for field team			3,300
International Travel			4,800
Subtotal			**9,600**
Other expenses			
Participants' / parents' wage loss	4	420	1,680
Printing, photocopying, etc.			400
Books/Literature			300
Library and interdepartmental			400
Communication (phone/fax/internet)			300
Miscellaneous (unforeseen)			435
Subtotal			**3,515**
Total Direct Cost			**71,553**
Institutional overhead (15%)			**10,733**
Total			**82,286**

*Four FRAs will work for 5 months with FTE.

** 12 CHRW of HDSS will work for 5 months with 50% effort equivalent to 30 person-months

***Riskshaw pullers/boatman will work for 5 months with FTE

4.3.2004

M. RAHMAN CHOWDHURY

Principal Investigator: Dewan Shamsul Alam

Detailed Budget for New Proposal

Project Title: *Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1) in rural Bangladesh*

Name of PI: Dewan Shamsul Alam

Protocol Number:	Name of Division: PHSD	
Funding Source: WB through NCOE Overhead (15%)	Amount Funded (direct): US$ 74,794	Total: 86,013
Starting Date: ASAP	Closing Date: 10 months from the date of start.	
Strategic Plan Priority Code(s):		

Principal Investigator: Dewan Shamsul Alam

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

Personnel
Dr. D. S. Alam will serve as the Principal Investigator (30% time commitment). He will ensure coordination and administrative supervision, and will provide overall scientific expertise on the development, and analysis of data and writing reports. Dr. George Fuchs will provide 5% time without salary support and will serve as a Co-Principal Investigator as well as technical adviser to the project. Dr. M. Yunus (10 % time commitment) will serve as one of the Co-Investigators and will provide scientific expertise in data analysis and interpretation and will also guide and facilitate implementation of the study. Dr. H. R. Chowdhury (5% time commitment) and Al-Fazal Khan (20% time commitment) will serve as Co-Investigators and will provide assistance in training of field workers and quality assurance of data collection. They will also facilitate implementation. Mr. M. A. Wahed (5%), as Head of the Nutritional Biochemistry Laboratory, will provide technical expertise in biochemical analyses. Dr. Liaquat Ali from BIRDEM will provide 10% time commitment but no salary support is requested from the project.

Field activities at Matlab
One Study Medical Officer at NOA level (100% time commitment) will be recruited to coordinate and supervise overall project activities. Fund is requested for one Study Nurse (GS5) to maintain clinic schedule, collect and process and blood samples. Four female Field Research Assistants (FRA GS3 level) will be recruited for conducting survey, communicating and inviting participants, and collecting dietary and anthropometric data during clinic visits. Each FRA will cover four villages. One Senior FRA (GS 4 level) will be recruited to supervise and monitor four FRAs and coordinate other field activities. He will also solve problem encountered by the FRAs in conducting their field activities. One laboratory technician (GS 3) will be hired for processing and storage of blood sample in the field laboratory. One data management cum office assistant (GS3 level) will be hired to compile data and check completeness of all data collection forms and questionnaires, also ensure timely arrangement of field transportation other logistic supports in the field. Data management cum office assistant will also work on data management and entry of data on computer. We need the support of the existing permanent Community Health and Research Workers (CHRW) of HDSS working in the study area as additional motivational force. We requested budget for supporting 50% salary of 12 Community Health and Research Workers of HDSS, Matlab for 5 months (approximate duration of field activity). Porters/rickshaw pullers/boatman will communicate with subjects very early in the morning so that subjects are brought to the clinic fasting. They will also work as messengers.

Equipments and supplies
Funds are requested for procuring two DINAMAP blood pressure monitor with cuffs. Also two SECA electronic weighing scales and two Stadiometers will be procured for measuring weight and height respectively. Funds have been requested for one computer and one printer for data management and entry. Costs for blood collection and serum storage containers have been included. Also the cost for purchasing one freeze for storage of blood specimens in the field laboratory is included. We requested fund for some office furniture such as filing cabinets for safe storage of data forms and other valuable materials required for the study.

Biochemcal tests
Budget for biochemical test has been estimated based on current rates. Blood glucose and lipid profile will be done will be performed in ICDDR,B. Plasma fasting insulin and IGF-1 concentrations which will be done at BIRDEM biochemistry laboratory.

Travel
Local travel will include travel between Dhaka and Matlab by the Investigators and important visitors using ICDDR,B Transportations. The study will also require extensive travel within Matlab study area by the field staff and supervisors to invite and motivate participants. ICDDR,B water transport (speedboats) will be used in Matlab for transportation of study participants from distant villages. Funds are requested for two international travels by the PI to attend relevant meetings/conferences. International travel costs will include airfare, per-diem and other admissible costs such as visa fees, in-transit per-diem or lay over costs, airport-hotel, taxis etc.

Other Support

Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration.
(DO NOT EXCEED ONE PAGE FOR EACH INVESTIGATOR)

Not required for this project.

Principal Investigator(*Last, first, middle*): ALAM, Dewan Shamsul

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Dewan Shamsul Alam	Senior Medical Officer

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Sir Salimullah Medical College, University of Dhaka, Bangladesh	M.B.B.S.	1982	Anatomy, physiology, biochemistry, pharmacology, medicine, surgery, etc.
University of Queensland, Brisbane, Australia	M.C.N	1992	Community Nutriton, Epidemiology, Biostatistics.
University of Queensland, Brisbane, Australia	M. Med. Sc.	1996	Community Nutrition, Nutritional Epidemiology, International Nutrition, Biostatistics,
Wageningen University and Research, Wageningen, The Netherlands	Ph.D. (Defense scheduled in June 2001)	1997- to date	Human nutrition and epidemiology

Courses attended

'Epidemiology, Statistics and Demography', offered by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), 30 March - 15 June, 1986.

Fourth International Graduate Course on Production and use of Food Composition Data in Nutrition: "Food Comp' '98", Wageningen 2-23 October 1998.

International course on body composition "Use of body composition techniques in laboratories and field studies" Wageningen 25-29 October, 1998.

SCHOLARSHIPS AND AWARDS

1999 Received student award as one of the finalists from Society for International Nutrition Research (SINR) at Experimental Biology '99 Meeting, Washington DC, 1999.

1997- ICDDR,B Staff Development stipend for Ph.D program in the Department of Human Nutrition & Epidemiology, Wageningen University, The Netherlands.

1991-93 Awarded Australian International Development Assistance Bureau (AIDAB) scholarship in 1991 to undertake a one year Master of Community Nutrition Program at the University of Queensland. Later the award was extended for another two-year period following the recommendation from the Department to undertake Master of Medical Science (Research Masters in Nutrition) programme at the same university.

1976-80 Enjoyed Board/University Merit Scholarship during the entire period of undergraduate studies.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with the present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Work experience

1982 – 1983 Medical Officer, In-service training, Bangladesh Health Services
1983 – 1984 Resident Medical Officer, Holy Ghost Hospital, Lagos, Nigeria
1985 – to date : Working with ICDDR,B, Dhaka, Bangladesh
Current position: Senior Medical Officer
Employer: Director, ICDDR,B Centre for Health and population Research, Dhaka, Bangladesh

Publications/Manuscripts submitted/in preparation

1. **Alam DS.** Effects of diarrhoea on growth of children under five years of age in rural Bangladesh. Masters Thesis, the University of Queensland, Australia 1996.

2. **Alam DS**, Marks GC, Baqui AH, Yunus M, Fuchs GJ. Association between clinical type of diarrhoea and growth of children younger than 5-year old in rural Bangladesh. Int J Epidemiol 2000;29(5):916-21..

3. **Alam DS**, van Raaij JMA, Hautvast JGAJ, Yunus M, Wahed M, Fuchs GJ. Effects of dietary fat supplementation during pregnancy and the first six months of lactation on vitamin A status of women and their infants (to be submitted).

4. **Alam DS**, van Raaij JMA, Hautvast JGAJ, Yunus M, Wahed M, Fuchs GJ. Validity of IVACG Simplified Dietary Assessment (SDA) in identifying pregnant and lactating women at risk for vitamin A deficiency in rural Bangladesh (to be submitted).

5. **Alam DS**, van Raaij JMA, Hautvast JGAJ, Yunus M, Fuchs GJ. Energy stress during pregnancy and lactation in rural Bangladeshi women: consequences for maternal nutrition (submitted to EJCN).

6. **Alam DS**, van Raaij JMA, Hautvast JGAJ, Yunus M, Fuchs GJ. Effect of maternal dietary fat supplementation during pregnancy and lactation on infant growth performance during the first six months of life (to be submitted).

7. **PhD Thesis**: Dietary fat supplementation of pregnant and lactating Bangladeshi women: the effect on vitamin a status and growth performance of infants, Division of Human Nutrition & Epidemiology, Wageningen University, The Netherlands (defence scheduled in June 2001).

Summary for Ethical Review Committee

Title of the Research Project: *Association between size at birth, and childhood blood pressure, fasting blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1) in rural Bangladesh.*

Principal Investigator: Dewan Shamsul Alam

Coronary heart disease (CHD), hypertension, and non-insulin dependent diabetes are leading causes of morbidity and mortality among adult population. The prevalence of these diseases has increased in developing countries, and it is believed that developing countries will face an epidemic of these diseases in near future. Following the initial report of Barker, additional evidence has accumulated to suggest that such diseases are disproportionately higher among those who were born smaller in size. It is thought that nutritional insult during a critical period of fetal life has permanent effects on wide range of structural, metabolic and physiologic functions. Therefore, low birth weight infants who survive through infancy and childhood are likely to be at greater risk for chronic diseases in later life. Experimental studies in animals, and human epidemiologic studies provide strong evidence to support the "Bareker's hypothesis" which is now commonly known as "fetal programming" for adult disease.

It is estimated that 20% of infants are low birth weight (LBW) globally, with Bangladesh having the highest rates of (50%) in the world. This high prevalence of LBW in Bangladesh is mainly attributable to intrauterine growth retardation resulting from maternal undernutrition. Because these LBW infants supposedly experienced intrauterine nutritional insult, they are believed to be at increased risk for coronary heart disease, hypertension, stroke, non-insulin dependent diabetes, and other metabolic abnormalities in later life. Recent studies have shown that higher blood pressure and some metabolic abnormalities are present among lower birth weight categories during their childhood as early as 4-8 years of age. However, most evidence is from developed countries where birth weight is relatively higher and low birth weight, especially IUGR rate is much lower. Therefore, it is also important to determine whether physiologic, metabolic and hormonal profile in low birth weight predictive of future risk for chronic disease are also prevalent in our population.

We propose a cross-sectional study design to examine the relationship between weight at birth and childhood blood pressure, fasting glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1). This study will be conducted in a cohort of approximately 420 children (currently aged 5-6 yrs) who participated along with their mothers in our previous study (1995-7) in which birth weight and other parameters of size at birth were meticulously collected. The mean birth weight was 2.51 kg and 48% were born low

আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র, বাংলাদেশ

সম্মতি পত্র

Title: Association between size at birth, and childhood blood pressure, blood glucose and insulin concentrations, lipid profile and insulin-like growth factor-1 (IGF-1).

P.I. Dewan Shamsul Alam

(শিশুর জন্মকালীন আকারের সাথে শৈশবের রক্তচাপ, রক্তে শর্করা, স্নেহ জাতীয় পদার্থ ইনসুলিন ও ইনসুলিন জাতীয় বৃদ্ধিকারক হরমোন-১ এর মাত্রার যোগসুত্র নির্নয় গবেষনা)।

প্রকল্পের অবস্থানঃ মতলব

আই,সি,ডি,ডি,আর,বি দীর্ঘদিন যাবত আপনাদের এলাকায় স্বাস্থ্যসেবা, ডায়রিয়া রোগের চিকিৎসা ও গবেষনা কার্য্যক্রম চালিয়ে যাচ্ছে। বহুমুত্র, উচ্চরক্তচাপ ও হৃদরোগ-উন্নত এবং উন্নয়নশীল উভয় দেশেই প্রাপ্তবয়স্কদের অসুস্থতা ও মৃত্যুর অন্যতম কারন। গবেষনায় দেখা গেছে, জন্মকালে শিশুর আকার ও পরবর্তীতে এসব রোগের উৎপত্তি এ দু'য়ের মাঝে এক দৃঢ় যোগসুএ রয়েছে। যদিও এসব রোগ মুলতঃ বয়স্কদের স্বাস্থ্য সমস্যা হিসেবে গন্য, কিন্তু এসব রোগের সুত্রপাত মানুষের জন্মলগ্ন থেকে বলে ধারনা করা হয়। অনেক ক্ষেত্রে এসব রোগের লক্ষনসমহ অথবা ঝুঁকি অল্পবয়সীদের মাঝেও দেখা যায়, বিশেষ করে যারা অল্প ওজন নিয়ে জন্মগ্রহন করে। যে সব শিশু জন্মকালে তুলনামুলকভাবে ছোট আকারে জন্ম নেয় তাদের মধ্যে প্রাপ্ত বয়স্ক অবস্থায় এসব রোগের প্রকোপ স্বাভাবিক আকারে জন্ম নেয়া শিশুর তুলনায় অনেক বেশী। আমাদের দেশে যেহেতু বেশীরভাগ শিশুই অল্পওজন নিয়ে জন্ম নেয় তাই ভবিষ্যতে তাদের বেলায় এসব রোগের ঝুঁকি ও তুলনামুলকভাবে বেশী হবার সম্ভাবনা। আই,সি,ডি,ডি,আর,বি একটি গবেষনা হাতে নিয়েছে যাতে আপনার সন্তানের রক্তচাপ সংক্রান্ত কোন অসুবিধা, রক্তে শর্করা ও শর্করা নিয়ন্ত্রনকারী পদার্থ সঠিক মাত্রায় আছে কি-না তা পরীক্ষা করে দেখা হবে।

আমরা আপনাকে এবং আপনার শিশুকে এ গবেষনায় সেচ্ছায় অংশগ্রহনের আমন্ত্রন জানাচ্ছি। আপনি আপনার শিশুকে এ গবেষনায় অংশগ্রহনের অনুমতি দিলে, আমরা আপনার শিশুর বর্তমান শারীরিক আকার ও রক্তচাপ মাপবো এবং খাদ্যাভ্যাস লিপিবদ্ধ করবো। বাচ্চার রক্তে শর্করা ও অন্যান্য বিপাকীয় পদার্থ নির্নয়ক উপাদানসমুহ সঠিক পরিমানে আছে কি-না তা জানার জন্য ৫ মিঃলিঃ বা ১ চা-চামচ পরিমান শিরার রক্ত বাহু থেকে সংগ্রহ করবো। ডাক্তার নিজে অথবা প্রশিক্ষন প্রাপ্ত এবং অভিজ্ঞ সেবিকা একজন ডাক্তারের উপস্থিতে খুব যত্নসহকারে রক্ত সংগ্রহ করবেন। আমরা যথাযথ সতর্কতার সহিত রক্ত সংগ্রহ করবো যাতে আপনার সন্তান তেমন ব্যথা না পায় এবং রোগ সংক্রমনের ঝুঁকি না থাকে।

আমাদের বিশ্বাস, এ গবেষণায় অংশ নিলে আপনার শিশুর স্বাস্থ্যের ক্ষতির কোন ঝুঁকি নাই। তবে অনেক সময় চামড়ার নীচে সামান্য রক্তক্ষরন হয়ে থাকে। যদি দৈবিক আপনার শিশুর বেলায় ইহা ঘটে আমরা যথাযথ ব্যবস্থা গ্রহনও চিকিৎসা প্রদান করবো। আমাদের পরীক্ষা-নিরীক্ষাকালে আপনার শিশুর যদি কোন অসুবিধা ধরা পড়ে, আমরা আপনাকে তা জানাবো এবং আমাদের পেশাগত কর্মীরা আপনাকে এ ব্যাপারে প্রয়োজনীয় পরামর্শ প্রদান করবেন।

এ গবেষনায় আপনার অংশগ্রহন সম্পুর্ন স্বেচ্ছামুলক। গবেষনা সংক্রান্ত কোন প্রশ্ন থাকলে আপনি যে কোন সময় জিজ্ঞেস করতে পারবেন এবং আমরা খুশীমনে তার উওর দিবো। আপনি ইচ্ছা করলে যে কোন সময়, এমনকি সম্মতি প্রদানের পরেও আপনার শিশুকে এ গবেষনায় অংশ নেয়া থেকে বিরত রাখতে বা প্রত্যাহার করতে পারবেন। এর জন্য আপনি বা আপনার পরিবার এ হাসপাতাল প্রদও সেবা ও চিকিৎসা থেকে বঞ্চিত হবেন না। আপনার ও আপনার বাচ্চার পরিচিতি ও সংগৃহীত তথ্যাদি সম্পুর্ন গোপন রাখা হবে, এমনকি গবেষনালব্ধ প্রকাশনাতে ও গোপনীয়তা রক্ষা করা হবে। আপনি যদি আপনার বাচ্চাকে আমাদের গবেষনায় অংশগ্রহনের অনুমতি প্রদানে আগ্রহী হন, তাহলে নিম্নে নির্ধারিত স্থানে আপনার স্বাক্ষর অথবা বাম বৃদ্ধাঙ্গুলির ছাপ প্রদান করে অংশগ্রহন নিশ্চিত করুন।

অনুমতিঃ আমাকে এই সম্মতি পত্রটি পড়ে শোনানো হয়েছে। গবেষনার বিষয়বস্তু, প্রয়োজনীতা, উপকারিতা, ঝুঁকি ইত্যাদি ঠিকমতো বোঝানো হয়েছে। আমি সবকিছু অবগত হয়ে স্বজ্ঞানে, স্বেচ্ছায় আমার বাচ্চাকে এ গবেষনায় অংশ গ্রহনের অনুমতি দিয়ে সম্মতিপত্রে স্বাক্ষর বৃদ্ধাঙ্গুলীর ছাপ প্রদান করিলাম।

তথ্য সংগ্রহকারীর স্বাক্ষর
তারিখঃ

অংশগ্রহনকারীর অভিভাবকের স্বাক্ষর
অথবা বাম বৃদ্ধাঙ্গুলীর ছাপ
তারিখঃ