DATA TRANSFER AGREEMENT

This agreement (hereinafter referred to as "Agreement") is made and entered by and between:

Shahroud University of Medical Sciences, Shahroud, Iran, ("Data Owner")

and the

Swiss Tropical and Public Health Institute ("Recipient")

Socinstrasse 57, 4051 Basel, Switzerland

Hereinafter jointly referred to as "Parties" and individually as "Party";

WHEREAS

- a) Data owner is the exclusive owner of the Shahroud Schoolchildren Eye Cohort Study (SSCECS) cohort data ("DATA");
- b) RECIPIENT, through Prof. Günther Fink, hereinafter referred to as "RECIPIENT SCIENTIST", has requested the DATA OWNER, through Prof. Mohammad Hassan Emamian, hereinafter referred to as "UNIVERSITY'S SCIENTIST", to provide RECIPIENT with the DATA for use by RECIPIENT'S SCIENTIST for the purpose of the RESEARCH PLAN;
- c) UNIVERSITY is willing, subject to the terms and conditions of this Agreement, to provide the DATA to RECIPIENT.

I. Definitions

- 1. DATA: The data and variables being transferred under this Agreement as specified in Annex I to this Agreement.
- 2. RESEARCH PLAN: The research plan specified in Annex II to this Agreement for which the DATA will be used.
- 3. EFFECTIVE DATE: The date of last signing of this Agreement.
- 4. INFORMATION: All information, know-how, and experience of UNIVERSITY supplied by DATA OWNER to RECIPIENT regarding the DATA, which is reasonably required by RECIPIENT for performance of the RESEARCH PLAN.
- 5. RESULTS: All data and results arising from performing the RESEARCH PLAN.

II. Terms and Conditions of this Agreement:

- 1. The DATA and INFORMATION provided is and remains the property of DATA OWNER and is made available as a service to the research community.
- 2. The RECIPIENT and the RECIPIENT SCIENTIST agree that the DATA: (a) is to be used only for the academic purposes as described in the RESEARCH PLAN; (b) will not be used for commercial purposes and (c) will not be transferred to a third party.
- 3. RECIPIENT'S SCIENTIST shall keep DATA OWNER'S SCIENTIST informed of the RESULTS.
- 4. It is expressly understood that DATA OWNER does not make any warranties regarding the DATA and specifically does not warrant or guarantee that the DATA will be accurate, be merchantable or useful for any particular purpose. DATA OWNER cannot and shall not be held liable for any claims or damages by applicant or any third party, in connection with or as a result of using the DATA.

- 5. RECIPIENT agrees in its use of the DATA to comply with all applicable international and national laws, statutes, regulations and guidelines.
- 6. RECIPIENT shall treat the INFORMATION confidential for the duration of this Agreement including any extension thereof and thereafter for a period of five (5) years following termination or expiry of this Agreement. Excluded from this obligation of confidentiality shall be any CONFIDENTIAL INFORMATION of which the RECIPIENT can reasonably demonstrate that it (a) was previously known to RECIPIENT, or (b) is, and/or becomes, publicly available during said five (5) year period through no fault of RECIPIENT, or (c) is independently and lawfully developed by the RECIPIENT. This obligation of confidentiality shall not apply to any disclosure required by law, provided that RECIPIENT shall notify UNIVERSITY of any disclosure required by law in sufficient time so that UNIVERSITY may contest such requirement, if UNIVERSITY so chooses.
- 7. RECIPIENT will share the preliminary as well as final results with DATA OWNER. DATA OWNER and other PIs of SSCECS will be offered co-authorship: all publications of the RESULTS must include 3 co-authors of DATA OWNER. First and last authors will however be RECIPIENT scientists.
- 8. This Agreement will become effective on the Effective Date and will terminate 3 years after the Effective Date. Parties can terminate this Agreement by giving a three (3) months prior written notice. Any clauses that will be expected or intended by its nature to survive the termination or the expiration of this Agreement, shall survive the termination or the expiration of this Agreement. Upon expiration or termination of this Agreement, the right to use the DATA and INFORMATION will automatically end and RECIPIENT will return or destroy all data received from UNIVERSITY.
- 9. This Agreement will be construed, governed, interpreted and enforced according to the laws of Switzerland. All disputes arising out of or in relation to this agreement will be brought before the competent court at the seat of the defendant party. In case of disputes the Parties will consult each other before taking legal action.
- 10. This Agreement represents this entire Agreement among the Parties with respect to the subject matter hereof, and may only be altered or amended by an instrument in writing signed by all of the Parties.
- 11. If any portion of this Agreement is in violation of any applicable regulation, or is unenforceable or void for any reason whatsoever, such portion will be inoperative and the remainder of this Agreement will be binding upon the parties.

IN WITNESS WHEREOF, the parties have executed this Agreement, in duplicate originals, as of the Effective Date.

Shahroud University of Medical Sciences

Date: June 24, 2021

Mb. Emamian

By: Prof. Dr. Mohammad Hassan Emamian Vice-chancellor for research and technology Swiss TPH

Date: 25-Jun-2021 | 12:46:42 CEST

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Ву:_____9FCAA9105B1F442...

Prof. Dr. Günther Fink Head of Household Economics and Health Systems Unit

ASSOCIATIONS BETWEEN BIRTH WEIGHT AND ADULT HUMAN CAPITAL IN LOWAND MIDDLE-INCOME COUNTRIES: A MULTI-COHORT STUDY

Date: June 24, 2021

By Prof. Dr. Ahmad Khosravi Head of Department of Epidemiology

Date: 25-Jun-2021 | 07:28:41 EDT

-DocuSigned by: Mcole Probst-Hensch D12E204B467847D...

By: _____D12E204B467847D... Prof. Dr. Nicole Probst-Hensch Head of Department of Epidemiology and Public Health

ANNEX I: DATA

The variables we would be interested in working with are listed below. Available data will vary by study.

1. Exposure

Birth weight in grams (Available for 303 schoolchildren)

2. Outcomes

Measures of:

-cognitive performance at age 10 or above (Not collected) -academic performance at age 10 or above (Not collected)

-educational attainment (number of completed years of schooling/education) (Available)

-other human capital at age 10 or above (Can be collected)

-earnings, wages, income or wealth in adulthood (Cohort participants now are students at 12-18

Y/O)

Is subject still in school/studying? (Yes) Is currently gainfully employed? (In most cases, No) HIV status (Not collected)

3. Perinatal covariates

Gestational age in weeks (Not collected)

Sex (Available)

Twin status (and indicator if other twin is in data set) (Available) Family income or other measures of socio-economic status (Available) Maternal age at birth (Can be collected) Maternal educational attainment; paternal educational attainment (Available) Maternal civil status at birth (single, married, etc) (All were married) Maternal smoking during pregnancy (Can be collected) Maternal alcohol consumption during pregnancy (Can be collected, almost all have no consumption)

Mother HIV status at birth (Can be collected, almost all were HIV negative)

4. Mediator variables lying on the path from birth weight to outcomes, measured between birth and age 5

Measures of:

-cognitive performance/development (Not collected but may be available from household records) -pre-academic skills (Not collected)

-executive function (Not collected)

-socio-emotional skills/development (Not collected)

<u>ANNEX II: PROJECT DESCRIPTION:</u> Associations between birth weight and adult human capital in low- and middle-income countries: a multi-cohort study

Background

According to the latest global estimates, 18 million infants were born low birth weight (LBW; <2500g) globally in 2010.¹ The primary causes of LBW are prematurity and intrauterine growth restriction (IUGR).² LBW infants are at increased risk of infant morbidity and mortality³ and are also more likely to experience linear growth faltering during childhood.⁴ There is also a growing literature indicating that LBW infants may be at greater risk for suboptimal neurodevelopmental outcomes during childhood,^{5, 6} with potentially important implications across the life course.

The developmental origin of health and disease (DOHaD) theory suggests that in utero exposures can increase the risk of adverse health outcomes later in life and across generations. Original studies showed that restricted foetal development, as measured by low birth weight, was associated with increased risk of adult hypertension, insulin resistance, obesity and other non-communicable diseases.⁷ Following Barker's original work,^{8, 9} positive associations between early life growth restriction and adult risk of chronic disease have been documented both in animal¹⁰ and human studies¹¹, even though disease trajectories among humans seem to be partially conditioned by early life catch-up growth.¹² However, more recent evidence suggests wider implications for immunological, mental health, and reproductive outcomes.^{13, 14} Foetal development may also affect human capital outcomes across the life course.¹⁵

Much less is known regarding the long-term implications of LBW on adult human capital outcomes such as educational attainment, cognitive measures or labour market outcomes such as earnings – as primary measures of socioeconomic well-being. In Lambiris et al. (2021 – under review), we present the results of a systematic review and meta-analysis of the economics and the biomedical literature designed to investigate this empirical association between birth weight and adult income. A second review is underway where we examine the association between birth weight and cognitive scores measured at age 10 and above.

Characterising the long-run human capital effects of adverse birth outcomes is important to estimate the broader societal impact of adverse birth outcomes and the potential benefits of interventions and policies to support vulnerable infants. This is particularly relevant in resource-poor settings. In both reviews we conducted, very few studies from lowor middle-income countries were identified. This raises concerns regarding the external validity of the estimates from high-income countries.

Project aims

To address this gap we are assembling a multi-cohort dataset that will allow us to assess the general relationship between birth weight and adolescent or adult outcomes in lowand middle-income settings.

We will explore how birth weight (unconditional on early life growth) is associated with long-term economic and human capital outcomes. We wish to investigate the associations documented in the literature with respect to the critical birth weight ranges (are effects constant, or mainly driven by kids in the tails of the distribution?), functional specification (e.g. linear vs. logarithmic) as well as the role of confounding in these links. Where available, we will also look at twins data to see if the main patterns can be confirmed in this (much smaller) subsample.

In addition, where suitable data on early life cognition or child/adolescent human capital exists, we will calculate how important their contribution is to the observed association between birth weight and long-term economic outcomes. This will allow us to make tentative arguments about the importance of competing causal pathways mediating the associations observed. Finally, where data is available, we will examine whether the observed associations are potentially linked to preterm birth versus slow fetal growth by using the fetal growth rate (birth weight divided by gestational age in weeks) as an alternative exposure to birth weight.

Data Sharing and Publication Plans

We will set up formal or informal data sharing agreements with all partners as needed. Only core variables will need to be shared in de-identified version. All collaborators will be offered co-authorship on the resulting paper (with maximum of 2 co-authors per site).

References

- 1. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *The Lancet Global health*. 2013;1(1), e26-36.
- 2. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics*. 1987;80(4), 502-511.
- 3. Lee AC, Kozuki N, Cousens S, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21(st) standard: analysis of CHERG datasets. *BMJ (Clinical research ed)*. 2017;358, j3677.

ASSOCIATIONS BETWEEN BIRTH WEIGHT AND ADULT HUMAN CAPITAL IN LOWAND MIDDLE-INCOME COUNTRIES: A MULTI-COHORT STUDY

- 4. Christian P, Lee SE, Donahue Angel M, et al. Risk of childhood undernutrition related to small-forgestational age and preterm birth in low- and middle-income countries. *International Journal of Epidemiology*. 2013;42(5), 1340-1355.
- 5. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG*. 2015;122(8), 1062-1072.
- 6. Sania A, Sudfeld CR, Danaei G, et al. Early life risk factors of motor, cognitive and language development: a pooled analysis of studies from low/middle-income countries. *BMJ open*. 2019;9(10), e026449.
- 7. Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of noncommunicable disease: implications for research and public health. *Environ Health*. 2012;11(1), 42.
- 8. Barker DJP. The fetal and infant origins of adult disease, 1992. BMJ Books: London.
- 9. Barker DJP, Osmond C. Infant-Mortality, Childhood Nutrition, and Ischemic-Heart-Disease in England and Wales. *Lancet.* 1986;1(8489), 1077-1081.
- 10. Van Abeelen AF, Veenendaal MV, Painter RC, et al. The fetal origins of hypertension: a systematic review and meta-analysis of the evidence from animal experiments of maternal undernutrition. *Journal of hypertension*. 2012;30(12), 2255-2267.
- 11. Arima Y, Nishiyama K, Izumiya Y, Kaikita K, Hokimoto S, Tsujita K. Fetal Origins of Hypertension. *Advances in experimental medicine and biology*. 2018;1012, 41-48.
- 12. Martin A, Connelly A, Bland RM, Reilly JJ. Health impact of catch-up growth in low-birth weight infants: systematic review, evidence appraisal, and meta-analysis. *Matern Child Nutr*. 2017;13(1).
- 13. Jazwiec PA, Sloboda DM. Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? *J Endocrinol*. 2019;242(1), T51-T68.
- 14. Nemoto T, Kakinuma Y. Involvement of Noncoding RNAs in Stress-Related Neuropsychiatric Diseases Caused by DOHaD Theory : ncRNAs and DOHaD-Induced Neuropsychiatric Diseases. *Advances in experimental medicine and biology*. 2018;1012, 49-59.
- 15. Bilgin A, Mendonca M, Wolke D. Preterm Birth/Low Birth Weight and Markers Reflective of Wealth in Adulthood: A Meta-analysis. *Pediatrics*. 2018;142(1).
- 16. Lambiris MJ, Blakstad MM, Perumal N, Danaei G, Bliznashka L, Fink G, Sudfeld CR. Birth weight and adult earnings: a systematic review and meta-analysis 2021 *Under review*