

ARIC MANUSCRIPT PROPOSAL

1.a. Full Title: Association between birthweight and cognitive function in middle age: the ARIC study

1.b. Abbreviated Title (length 26)

Birthweight and Cognition

2. Writing Group (list individual with lead responsibility first):

Antonio Jose Leal Costa

Pauline Lorena Kale

Ronir Raggio Luiz

Moyses Szklo

Kate Tilling

Contact Information for Lead Author:

Moyses Szklo

410-955-3462

mszklo@jhsph.edu

3. Timeline:

An initial draft of this manuscript is expected in 6 months.

4. Rationale:

The association of poor fetal nutrition and chronic diseases in adult life has been documented in a number of studies (Barker, 1998, 1999; Gillman, 2002). There is considerable evidence that malnutrition in early life can have an adverse effect on the developing brain (Martyn *et al*, 1996). The association between birthweight and cognitive development has been consistently observed within European cohorts born during different periods in the 20th century (Jefferis *et al*, 2002). In the Aberdeen Children of 1950's cohort study, growth *in utero* and during childhood were correlated with later cognition scores (Batty *et al*, 2004). Birthweight was associated with cognitive performance in young adult life in a historical Danish men cohort (Sorensen *et al*, 1997). Such findings have been supported elsewhere and imply a role for childhood nutrition (Richards *et al*, 2001, 2002). The association between weight at birth and later cognition through childhood, adolescence and early adulthood could not be explained by confounding by (and no effect modification was seen with) social factors and postnatal growth (Jefferis *et al*, 2002; Richards *et al*, 2002). Importantly, Richards *et al* (2001) observed that the association between weight at birth and later cognition was evident across the whole spectrum of birthweight, rather than being confined to an extreme group. The association between fetal growth and cognitive function in later adult life, however, remains uncertain (Richards *et al*, 2001, 2002; Martyn *et al*, 1996).

The fetal origin of adult disease hypothesis has been explored in the ARIC study (Tilling *et al*, 2004), but the association between birthweight and cognition has not yet been analyzed. In the ARIC study, cognitive performance was evaluated twice at ages 48-67 and 54-73 years old at visits 2 and 4 of the cohort (Mosley *et al*, 2005; Elkins *et al*, 2005; Moraes *et al*, 2003, 2002, 2001), thus allowing the investigation of its relationship to birthweight.

The purpose of the current study is to investigate the association between birthweight (ascertained at visit 4) and cognitive functioning in the ARIC cohort. We also intend to evaluate potential confounding factors based on previous ARIC analyses as well as potential effect modifiers, such as childhood socioeconomic environment, adult sociodemographic and anthropometric factors, and vital exhaustion.

5. Main Hypothesis

There is an independent association of low birthweight with lower cognitive functioning as well as cognitive decline between visits 2 and 4.

6. Data

Analysis will be based on the cognitive testing results done in visits 2 and 4, and on the information obtained on birthweight in visit 4.

Outcome data - Cognitive performance evaluated using the Delayed Word Recall test, the Digit Symbol Subtest of Wechsler Adult Intelligence Scale-Revised and the Word Fluency Test (Moraes *et al*, 2003) - will be obtained from visits 2 and 4 examinations.

At the 4th visit, the participants were asked to recall their exact birth weight. Those who were unable to recall their exact birth weight were asked whether they could remember whether it was low (< 5.5 lbs), medium (5.5-9 lbs) or high (>9 lbs) (Tilling *et al*, 2004). Both recalled exact birth weight and recalled birth weight category will be used as exposure variables.

Most covariate data will be obtained from visits 2 and 4. Additional covariate data (age, adult level of education and income) will be ascertained from Visit 1 examination. Covariates are as follows:

Childhood socioeconomic environment variables: maximum parental education at participants' birth or maximum education of the two adults caring for the child if these were not the parents.

Adult sociodemographic and anthropometric variables: age, gender, ethnic group, education level, field center, income, occupation, marital status, perceived health status, and body mass index.

Behavioral factors: smoking status and ethanol use.

Vital exhaustion: assessed by the Maastricht Questionnaire.

Analysis

Due to the long time interval between exposure and outcome, the potential for selective survival must be considered in this study. Additionally, the use of birth weight data self-reported at ages 54 to 73 years old may result in misclassification of the exposure variable. However, as mentioned by Tilling *et al* (2004), other studies have found high correlation coefficients between actual and reported birth weight.

Unadjusted mean and percentile values of cognitive test scores will be examined in relation to birthweight (these categories will be selected prior to starting the analyses). Selection of potential confounding variables and effect modifiers will be based on examination of associations with birthweight and cognitive function, by means of stratified analysis and/or regression models.

Linear regression modeling will be used to analyze the association between birth weight and average cognitive function as well as changes between visits 2 and 4, as was done in past ARIC papers (Wong *et al*, 2002; Moraes *et al*, 2001). We will also examine the relationship between birthweight and low levels of cognitive functioning using logistic regression and the same cut-off point for the latter as that used in a previous manuscript (Szklo *et al*, 1996).

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