A Life Course Study of Early Childhood Height Growth and
Adult Working Memory and Depression Outcomes

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ABSTRACT

Early Childhood Height Growth in Relation to Working Memory and Lifetime Major Depressive Disorder Outcomes in Middle Aged Adults

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Evidence has been mounting that exposures during fetal development and early postnatal life are important determinants of many adult health outcomes including. diabetes, obesity and cardiovascular disease. Critical periods of early development have been identified for certain outcomes. Early life factors are suspected as having a role in cognitive and psychiatric outcomes, but research to date is limited.

Birth weight, considered a marker for fetal development, has been positively associated with cognitive abilities. A few postnatal studies provide evidence that early childhood height growth, an indicator of overall development, is also positively associated with cognitive abilities in adults under age 25 years.   There has been no research on early childhood height growth and cognitive outcomes in middle age adults. Low birth weight has also been associated with a spectrum of neuropsychiatric disorders, including, in one study, affective disorders. There are no known studies of early childhood height growth and neuropsychiatric disorders.

With this background, I made two hypotheses. First, I hypothesized that early childhood height growth is positively associated with working memory ability in middle age adults.

Second, I hypothesized that early childhood height growth is inversely associated with lifetime major depressive disorder in middle age adults.

I also explored effect modification by sex and by small for gestational age status.

I tested these hypotheses using data from the Early Determinants of Adult Health (EDAH) study and its sister study Fetal Antecedents of Major Depression and Cardiovascular Disease (MDCVD). These studies were adult follow-up studies of two birth cohorts recruited in the 1960's: the Child Health and Development Studies (CHDS) and the New England Family Study (NEFS); both followed subjects from birth through childhood. Birth length and successive early childhood height measures were available enabling a study of three height growth periods, birth to 4 months, 4 months to 1 year and 1 to 4 years. The adult follow up study included 4 measures of different aspects of working memory ability as well as a structured interview that assessed neuropsychiatric outcomes including lifetime major depressive disorder.

We found some evidence that early childhood height growth was positively associated with adult working memory ability in specific growth periods. Results of the analysis of early childhood height growth and adult lifetime MDD do not support the association between early   childhood   height   growth   and   lifetime   MDD.

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A Literature Review on the Associations Between Height Growth

and Cognitive Abilities

Introduction

The relationship between attained height and cognitive abilities has been studied extensively in various populations and results are consistent in finding a positive association. There is less evidence regarding the relationship between height growth and cognitive abilities although results are fairly consistent in finding a positive association. The biological mechanisms underlying associations between height or height growth and cognitive abilities have not been elucidated. In general, height growth may reflect favorable circumstances for overall development, including brain development. More specifically, brain development, like height growth, depends on insulin-related growth factor (IGF) levels.[1-3] While these hypotheses are intriguing, they have not yet been tested in humans.

Current knowledge on the relationship between height growth and cognitive abilities in humans relies largely on epidemiology studies. The studies vary widely in design and methodology and the ages when height growth and cognitive abilities are measured. Because of these differences, evaluating and interpreting study findings is challenging.   A critical review of this literature is important in order to assess the quality of evidence for a causal relationship between height growth and cognitive abilities and to help establish whether there are critical periods of height growth associated with cognitive abilities.

Moreover, greater clarity is needed on the question of whether associations between height growth and cognitive abilities at early ages persist as a child reaches adulthood.

The first section of this paper discusses the design and methodological features that warrant attention in studies of attained height, height growth and cognition. Next, the literature search process for this systematic review is described. All relevant studies are then reviewed in the context of the design and methodology features. The review ends with a discussion of insights from these studies and recommendations for future research directions that will increase and enrich knowledge of this relationship.

Note that 'attained height' will be referred to as 'height' in this article.

Study Design and Measurements

Temporality

Cross sectional designs are used in most studies that examine the relationship between height and cognitive abilities. Height is a measure of cumulative prenatal and postnatal height growth, providing a longitudinal element to the cross sectional design. However, this only holds true as long as height increases or is stable. The longitudinal element disappears when adult height begins to decline, typically around age 40 years.[4] Since at least two height measures are needed to calculate height growth, cross sectional designs cannot analyze the relationship between height growth and any outcome except for total prenatal and postnatal growth.

Longitudinal cohorts are used to evaluate the relationship between height or height growth and cognitive abilities. Many prospective longitudinal studies are based on data from birth cohorts that follow individuals from birth through childhood and, in some cases, adolescence and adulthood. Retrospective longitudinal studies measure cognitive abilities in a cohort and this data is analyzed in relation to earlier height growth measures available in national health records.

While causal inference is improved by use of longitudinal instead of cross sectional study designs, loss to follow up is an important issue in prospective longitudinal studies. Loss to follow up tends to increase with the length of the follow up period. If loss to follow up is differential with respect to the exposure variable, then the results may be biased. Thus these studies must compare the characteristics of the follow up population with those of the original cohort in order to assess threats to internal and external validity.

Longitudinal studies are essential for identifying periods when the relationships between height growth and cognitive abilities are strongest. Identification of these 'critical' periods depends on availability of height and outcome measures at various points during the life course. If available, birth cohorts and national health records are useful since they usually have several childhood height measures that can be used to assess height growth. Since the hypothesized timing of a critical period may not coincide precisely with height growth periods available from data sets, it can be difficult to test hypotheses directly. However, where available height growth data overlap with a hypothesized critical period, the results may still provide some evidence of causal associations. These results may be attenuated

from the true relationship. Advanced statistical methods are available to assist with interpolation of height measures for height growth periods of interest.

Measurements

Height. Height is a measure of cumulative prenatal and postnatal height growth. It is measured at birth and regularly during childhood at clinic visits. Measurement errors largely result from improper positioning of the head, and subject cooperation.[5,6] These measurement errors are likely non-differential with respect to cognitive abilities.

For analysis purposes, height measures, especially in children, are often transformed into standardized values to make them easily comparable in a given population and across time. An individual's height measure is assigned a 'z-score', a non-dimensional measure that expresses the distance, positive or negative, from a mean in standard deviation units. The height z scores can be translated into height percentiles. To accurately assign z-scores, it is important that the population used to construct the standardized distribution is the source population for the study. If not, then the percentile differences between height measures are inaccurate though rank order is preserved.

Height Growth. Height growth is the height difference at the beginning and the end of a growth period. With standardized measures, height growth can be measured as the difference in z-scores or corresponding height percentiles between the beginning and end of the growth period. In some children, height growth occurs in small spurts alternating with periods of lower growth velocity every month or two months.[7] The result is that

height growth measures, while correct, may not accurately characterize the underlying height growth trajectory.[8]

Cognitive Abilities.   In this review, the term 'cognitive abilities' refers to the construct of general intelligence or IQ.   This construct is measured by validated instruments such as the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Intelligence Scale for Children (WISC), and Raven's Progressive Matrices.   Some studies use intelligence test subsections such as verbal or performance IQ modules.   These subsections measure abilities that are correlated with general intelligence but represent only a portion of the intelligence construct.[9]   Measurement error occurs when subjects test below their ability level due to depression, illness or distraction, or if testing conditions are substandard.[10] Tests may not have construct validity for minority groups and often have not been validated for these groups.[11]

Cognitive abilities can be conceptualized as a distributed network of brain functions.[8] Evidence suggests that specific brain areas and circuits related to these functions have different critical periods of development.[12]   For example, working memory functions are partly located in the hippocampus.   This brain area develops largely by age 12 months and somewhat further into the second postnatal year except for myelination which continues throughout development.[13] . Research on the relationship between height growth and specific abilities during hypothesized critical periods may help to map brain areas to specific cognitive abilities.

Academic achievement tests have been used to measure cognitive abilities in some situations. Cognitive abilities and academic achievement are highly correlated.[14] Academic achievement depends not only on intelligence but also characteristics such as socioeconomic status (SES) and personality.[15] Thus, academic achievement and intelligence are not the same construct and investigators must be careful in choosing outcome measures and interpreting the results of studies focused on academic achievement.

Socioeconomic Status. SES is a measure that indicates access to resources, power and control and is strongly associated with health outcomes[16], including height[17,18] and cognitive abilities.[19,20] SES is measured by one or more variables, the choice of which likely depends on available data. In many height growth studies the parental SES is measured around the time of a child's birth. Paternal income and occupation variables are often used as SES measures. Other measures include maternal education, family income, family wealth, living conditions and neighborhood. Often several of these variables are included in an analysis or are combined into a single variable to represent the SES construct. With adult outcomes, adult SES may also be important in some health studies. However, in studies of height growth and cognitive abilities, statistical control for adult SES is problematic because both childhood SES and adult cognitive abilities may predict adult SES. This will render adult SES as a collider variable that, if controlled, may distort the relationship between height growth and cognitive ability. See Figure 1 below.
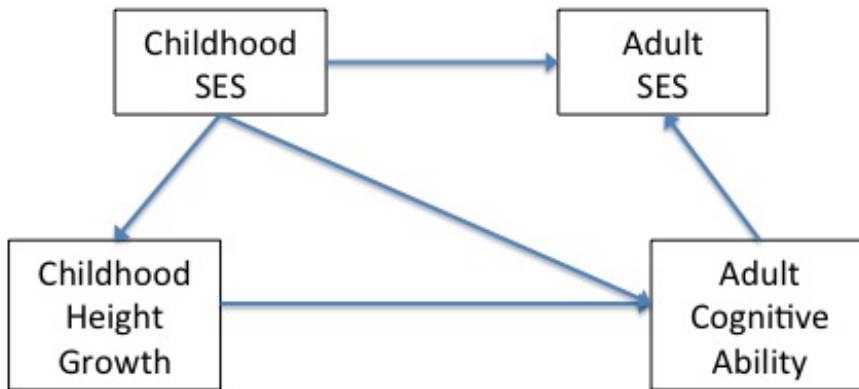
Figure 1. Adult SES as a Collider Variable

Other Confounders. The relationship between height and cognitive abilities may be confounded by variables other than SES. These include maternal age, paternal age, maternal intelligence, parity and alcohol use during pregnancy.[21]

Important Considerations in Data Analysis

Introduction

Special considerations apply to the analysis of the relationship between height growth and cognitive abilities. These considerations are related to model selection and effect modification. The section below outlines these topics and how they apply to the statistical modeling of the relationship between height growth and cognitive abilities.

Study Period Length and Model Selection

The relationship between height growth and cognitive abilities can be analyzed by several methods such as linear or logistic multivariate regression, and marginal structural models

(MSMs). Each of these models accommodates confounder control and effect modification analysis. In some complex cases, MSMs offer advantages over multivariate regression models. MSMs allow for assessment of direct and indirect effects of the independent variables on the outcome. They include auto-correlated error structures among the independent variables and so are able to isolate the relative contribution of each variable to the outcome.[22] A study assessing the relationship between preeclampsia and neonatal outcomes provides an example. The MSM analysis separated the direct and indirect effects of preeclampsia on the neonatal outcome. This included the separation of the effects of potential confounders of the various relationships between the exposure, mediator and outcome variables. This confounder treatment is important because in this case, confounders of the preterm birth/neonatal outcome association, such as caesarian section, are also related to preeclampsia status. With this situation, more traditional statistical 'adjustment' for these confounders could bias effect estimates [23]

Effect Modifiers

Sex Differences. Neuroscience studies have shown that brain development patterns and brain function at maturity differ by sex.[24] Some of these differences are in areas and networks of the brain related to cognitive ability.[25-27] Given these differences, sex is a possible modifier of associations between height growth and cognitive abilities.

Small for Gestational Age Children (SGA). Children born in the lowest 10% of the birth weight for gestational age distribution are defined as small for gestational age (SGA). Most SGA children have rapid catch-up height and weight growth in the first two postnatal years

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and mean intelligence around the population mean at later ages.[28] In contrast, rapid infancy and early childhood height growth in the general population has been associated with cognitive abilities above the population mean[29], implying a possible pattern differences between SGA and non-SGA children. The combined population-based result may obscure the true relationship for these two groups. Therefore SGA status is a potential effect modifier.

Methodology Summary

The study of height growth and cognitive abilities is complex and there are a number of methodological issues that need to be considered.   Datasets for these studies must be carefully considered to assure that the set of variables available for the analysis are appropriate and adequate.   This includes height measures for the appropriate height growth periods, effect modifiers, SES and appropriate cognitive tests.

Literature Search Procedures

The literature search was performed in two phases and completed on July 5, 2013. The first phase of the literature searches identified papers on the relationship between height or height growth and cognitive abilities. Figure 1 shows the major search terms and results from Ovid Medline. This resulted in a list of 418 articles. We selected papers based on the following criteria: an exposure variable that is a measure of postnatal attained height or height growth, an outcome variable that is a measure of cognitive ability, an individual level analysis of the relationship between these exposure and outcome variables, a sample

representative of the general population and a location in a high income country or population. Based on these criteria, the selected articles total 15, representing 14 studies.

A second phase identified papers on the relationship between height growth and cognitive abilities outcomes in population-based cohorts from the Psych Info database. Figure 1 shows the major search terms and results for the Psych Info search. This resulted in 582 articles; 301 overlapped with those in the PubMed literature search. Of the remaining 281 articles, 1 was added to the review after applying the selection criteria described above. Finally, one article was sourced from a list of related citations in PubMed. In total, 16 articles were included in the review, representing 15 studies.

As noted above, certain studies were excluded from the final literature reviews. First, studies focused on children with diagnosed disorders known to affect height growth or cognitive abilities were excluded since these reflected different mechanisms affecting these variables. An example of these diseases is achondroplasia, an autosomal dominant genetic disorder causing dwarfism[30] and juvenile rheumatoid arthritis that slows growth rates.[31] Second, we excluded studies from low income countries because, relative to high income countries; these populations have a far greater prevalence of severe malnutrition leading to stunting[32] and higher rates of infection, characteristics related to height growth and cognitive development.[33]   These different environments make if difficult to construct meaningful individual level comparisons with subjects in high-income countries. Third, commentary and review articles were excluded.   Fourth, studies with academic achievement as the outcome were excluded.

Literature Review

Height Growth and Cognitive Abilities

Introduction. This section reviews the associations found between height growth and cognitive abilities in 6 studies. These studies include 50 analyses of various growth periods, cognitive abilities measures and ages at cognitive ability measurement. The design, measurement and methodology features that underpin the quality and utility of the results are discussed following the review. Detailed descriptions of these studies can be found in Exhibit 1. A graph of study results by age and cognitive ability measure can be found in Figure 2.

This review is organized by the age of the subject when cognitive abilities were measured:

- Childhood: ages 4.5-11 years,
- Adolescent: ages 12-17 years, and
- Adulthood: ages 18-43 years.

Within these sections, results are organized by height growth period:

- Infancy: birth to age 2 years,
- Early childhood: ages 2 to 5 years,
- Later childhood: ages 6 to 11 years, and
- Adolescence: ages 12-17 years.

In a few analyses the timing of exposure periods and outcome measurement does not fit neatly within these categories. These analyses were placed in the closest matching category.

Two analyses were excluded from this section of the review. The Pearce study[34] is excluded because the outcome was measured during the exposure period, resulting in a confusing temporal order. The Wilson study is excluded because the height growth variable included observations with different age ranges, rendering interpretation impossible.[35] These issues render meaningful inference impossible based on the information provided.

Childhood Cognitive Abilities Outcome Analyses In the 5 studies including childhood cognitive abilities outcomes there were several exposure periods and ages at which outcome was measured .

Infancy Height Growth. The Heinonen[29] and Yang[36] studies both examined height growth in infancy. Heinonen found that two height growth periods between birth and age 20 months were associated with visual-motor integration scores at age 4.5 years, but not with general reasoning, verbal competence or language comprehension scores. Yang found that height growth from birth to age 12 months was positively associated with full-scale IQ scores at age 6.5 years and relationships were slightly stronger for verbal IQ than performance IQ subscales.

Early Childhood Height Growth. Positive relationships were also found in analyses of early childhood height growth and cognitive abilities. In the Heinonen study, height growth between ages 20 and 56 months was positively associated with verbal competence and language comprehension at age 4.5 years, but not with visual motor integration or general reasoning.[29] In the Yang study, height growth between

ages 1 and 5 years was positively associated with full-scale IQ scores at age 6.5 years with the strength of the association equivalent between verbal IQ and performance IQ subscales.[36] In the Montgomery study, height growth from ages 22 months to 5 years was positively associated with digit recall test scores, a measure of verbal working memory[37], at age 10 years.[38] The Richards study provided evidence that height growth between ages 2 and 4 years was associated with intelligence scores at age 8 years.[39]

Height Growth in Late Childhood. The Silva study included the only analysis of late childhood height growth in relationship to childhood cognitive ability. Both the regression and MSM analyses found that an association between height growth from ages 5 to 10 years and general cognitive function measured at age 10 years.[22]

Adolescent Cognitive Abilities Outcome Analysis. Only the Richards study examined cognitive abilities measured during adolescence. This analysis indicates that height growth from ages 8 to 15 years is not associated with general cognitive abilities measured at age 15 years.[39]

Adult Cognitive Abilities Outcome Analyses. Both the Raikonnen and Richards studies included analyses of the association between height growth and adult cognitive abilities.

Height Growth in Infancy. An analysis from the Raikonnen study examined infant height growth and cognitive abilities in conscripted men with a mean age of

approximately 20 years.   Height growth between ages 6 months and 2 years was positively associated with all three measures of cognitive abilities: verbal reasoning, visuospatial reasoning and arithmetic reasoning.

Early Childhood Height Growth. In the Raikonnen study, height growth between ages 2 and 7 years was positively associated with verbal and visuospatial reasoning but not arithmetic reasoning.[40]

Later Childhood Height Growth. In another Raikonnen analysis, height growth between ages 7 and 11 years was not associated with any of the three cognitive ability measures.[40]

Adolescent Height Growth. The final analysis from the Raikonnen study indicated that height growth between ages 11 and age 20 years was positively associated with all three cognitive ability measures.[40]   The Richards study found associations between height growth from ages 15 to 36 years and cognitive abilities at age 26. When an outcome variable is measured during the exposure period, the result is impossible to interpret. However, in this study, the authors correctly chose to use height measured at age 36 for two reasons. First, height at age 26 years was self-reported and these measures are typically over-estimated.[41] Height was measured at age 36 years by a clinician and therefore highly likely to be valid.   Given that height growth into the 20's is unusual[42] and that height does not begin to decline

until age 40[4], the measurement of height at age 36 is a valid proxy for height at age 26.

Socioeconomic status and potential confounder variables. All of the analyses described above included statistical control for the confounding effects of family socioeconomic status (SES) at or near the subject's birth date. The SES variable differed between studies but all reflect the underlying construct of SES. Statistical control for SES after birth or infancy was not included in any analysis. Except for the Montgomery study, all of the analyses controlled for most though not all of the other confounders described above. The Montgomery study controlled for SES but not any of these other confounders.[38]

Study Populations. Four height growth studies are based on data from birth cohort datasets and, of these, three studies utilize the British birth cohorts. The Richards study is based in the 1946 British Birth Cohort and the multiple measures of height growth available make this the source of several analyses used in this study.[43] The Montgomery and Silva studies were both based on data from the 1970 British Birth Cohort.[22,38] The remaining birth cohort was based in Finland and was also the source of several analyses given the multiple measures of height during childhood.

The source populations for the birth cohorts were the general public in the study area. For instance, all children born in a certain week in April, 1970 in the England, Scotland and Wales were enrolled in the 1970 British Birth cohort.[22] These cohorts did exclude some subjects such as those from multiple births, or in the case of the 1946 British Birth Cohort

'illegitimate' children, presumably children of unwed mothers.[39] For studies using birth cohort data, certain groups of subjects were later excluded or over-sampled. Montgomery's study subsample from the 1970 British Birth Cohort over-sampled the children born SGA, post-term or as part of a multiple birth. The Raikonnen study analyzed only males from the Helsinki Birth Cohort that had also been conscripted into the Finnish armed forces.

Two study cohorts used different sampling strategies. The Yang study was based on a convenience sample of children whose mothers had enrolled in a randomized trial of a breastfeeding intervention. The children had at least 37 weeks gestation at birth and had a birth weight of at least 2500 g.[36] The Heinonen sample has similarities to a clinical sample as the majority of its participants had been admitted to a NICU with others recruited at birth at local hospitals. The population was later limited to children born at term and without major impairments, mental retardation or developmental delay.[29]

Loss to follow up. Loss to follow up and missing data were characteristics of all of these studies and differences existed between those excluded and included in these analyses. The proportion of subjects excluded from analyses due to loss to follow up or missing data ranged from 28% at age 56 months in the Heinonen study[29] to 61% at age 26 years in the Richards study.[39] The extent of differences between excluded and included subjects varied widely by study. Information on differences between the participants and non-participants were limited. From the information available, there were no discernable common characteristics among the non-participants.

Measures of height and height growth. Health professionals measured heights. Heights reported at specific ages were adjusted for actual age on the measurement date in the Heinonen study only.[29] Height was treated as a continuous variable in all studies except for the Richards study which categorized height into 5 levels at each age.[39] Height measures were standardized in the Montgomery and Raikonnen using z-scores calculated separately by sex. The basis for the z-scores was not reported in the Montgomery study and was based on measurements from the entire birth cohort in the Raikonnen study.[38,39]

The height growth measures differed between studies. In the Heinonen and Raikonnen studies, the growth measures were standardized residuals from linear regression of previous height measurements for a subject. In the Montgomery study, height growth was measured as the differences in z-scores at the beginning and end of the height growth period. In the Silva and Richards studies, height growth was not measured *per se*, but the associations of height growth with cognitive abilities were ascertained from the statistical analysis designs as described below.

Measures of outcomes. Outcome measures differed between studies, reflecting differences in age at measurement and in the underlying construct of cognitive abilities. The Yang study and Richard's analysis at ages 8 and 15 years used measures that represented a construct of general intelligence. Yang used a full-scale IQ measure with verbal IQ and performance IQ subscales and Richards used a broad variety of cognitive ability measures combined for a single score.[36,39] The Heinonen, Yang, Montgomery, and other Richards analyses analyzed relationships with specific cognitive abilities such as digit recall, reading

comprehension and verbal or performance IQ.[29,36,38,39] The Silva study used a composite measure derived by principal components analysis to represent cognitive function. The underlying measures included a general IQ test and 3 achievement tests.[22] The achievement tests represent a different construct than the ability tests so that the outcome measure in the Silva study does not isolate cognitive ability.

Statistical analysis. Multivariate regression models were utilized in all height growth studies to examine the relationship with cognitive abilities. The Yang study used generalized estimating equations (GEE) regression analysis to adjust the standard errors for data clusters by hospital and other clinics where subgroups of the sample were measured.[36]. A MSM was used in the Silva study to ascertain direct and indirect effects of a number of variables, including height growth.[22] The Richards study categorized heights and used the means of these categories in the regression analyses rather than individual level variables.[39] Height measures were transformed into trajectories in the Yang study.[36]

Most studies included prior height growth or height at the beginning of the growth period as a covariate to control for the possible relationship of prior prenatal and/or postnatal height growth with the cognitive abilities outcome. In Richard's analyses of outcomes at ages 8 and 15 years, these height variables were used to determine periods when height growth was associated with cognitive abilities.[39] Potential confounders were included as covariates in the regression and structural equation models. Effect modification by sex or SGA was not examined in any of the studies except in the Yang study.

Summary. The six studies reviewed above provide some evidence of relationships between several height growth periods and various cognitive abilities. These studies were soundly designed with good control for SES and other confounders, appropriate modeling and statistical analyses, diverse and valid outcome measures and, in most cases, a population-based sample appropriate for public health studies. Height growth measures varied though it is unclear whether height measures at given age points have been adjusted for the actual age at the time of measurement, a study weakness that could lead to biased results. High levels of loss to follow up are also a weakness of these studies, especially because characteristics of those followed up differed from those of the original cohort, making generalization of results difficult. These weaknesses suggest that caution be used in interpreting results.

Height and Cognitive Abilities

There were 15 analyses of the relationship between height and cognitive ability and all showed positive associations. While these studies are mainly cross-sectional, there are a few longitudinal and repeated cross sectional study designs that offer more causal perspectives. Detailed descriptions of these analyses can be found in Exhibit 2.

There are 2 longitudinal studies of height and cognitive abilities. The Fisch study showed that children with greater height at ages 1 and 4 years had higher IQs measured at ages 4 and 7 years.[44] The Humphreys study measured children's height and cognitive ability on an annual basis from ages 8 to 17 years. In longitudinal analyses there are consistent positive correlations between height and cognitive abilities throughout this age period. The highest

correlations are between height at ages 8 to 11 years and cognitive ability at age 12 years. The correlations were generally higher in females than males. The Fisch analyses controlled for SES while the Humphrey's study did not. [44] [45]

Three studies feature repeating cross sectional analyses. The Wilson study analyzed children at ages 6 to 11 years and 12 to 17 years using NHANES data. For females, the relationship between height and intelligence score was higher for the older group. For males, relationship strength was similar between the age groups.[35]   In contrast, the Humphreys study showed that cross sectional correlations in females were highest at ages 8 to 13 years and then declined from ages 14 to 17 years. Humphreys also found that correlations in males varied from year to year but were generally consistent with the Wilson results.[45]   The only design difference was that the Wilson study controlled the analysis for SES.

The Richards analyses show that cross-sectional relationships between height and cognitive abilities were higher at ages 26 and 43 years than at ages 8 and 15 years. However, because the cognitive ability construct was limited to verbal abilities only at the older ages, it is difficult to know if this difference or the age difference is the cause of the varying relationship strengths.[39]

There are 14 cross sectional analyses across a range of ages. There were 5 analyses of the childhood period from ages 4.5-11 years[35,39,46-48], 4 analyses of the adolescent period from ages 12-17 years)[35,39,45,49] and 5 analyses of the adult period from ages 18 through a mean

age of 43).[39,50-52] Three of these adult analyses used data on military conscripts at or around age 18 years.[50-52]

Each cross sectional analysis used either correlation or multiple regression statistical methods to describe the height and cognitive abilities outcome except for one study that provided only a graph of the relationship.[52] All study samples were population-based: 8 analyses were sourced from birth cohorts, 3 from military conscript studies and 2 from the National Health Examination Survey (NHANES) in the US. Other samples were sourced through schools and advertising. Loss to follow up in the birth cohort studies could threaten external validity of those results, a problem previously discussed in the height growth section above.

Major differences in confounder control, especially SES, and the cognitive ability constructs make it difficult to compare results. This difficulty is compounded by differences in categorizations of variables, the use of standardization and statistical methods. Even with these differences, it is notable that the results are consistently positive in all analyses.

Discussion

Based on the studies reviewed, the relationship between height growth and cognitive ability outcomes is dependent on the growth period measured as well as the type of cognitive ability. Given this complexity and the quality of the studies, the number of studies reviewed here can only be observed as preliminary evidence with many other relationships to be tested or possibly replicated.

More specifically, the evidence is mixed for a positive relationship between height growth in the early postnatal months and both verbal and non-verbal abilities measured at several later ages. There is evidence of a positive relationship between height growth in infancy and visual-motor integration. A positive relationship may also exist between height growth from late infancy to middle childhood and verbal abilities measured at various ages. There is also evidence for a positive relationship between height growth during middle childhood and working memory ability measured at age 10 years. However, the evidence for a positive relationship between height growth in this middle childhood period and non-verbal abilities is mixed.

There is little evidence supporting a relationship between height growth in later childhood and any cognitive abilities measures. Height growth during adolescence is positively associated with early adult cognitive ability measures.

The consistent relationship between height and cognitive abilities across a spectrum of ages and cognitive ability measures supports the evidence for a positive relationship between height growth and cognitive abilities. However, several of these analyses lack confounder control and results may reflect residual confounding by SES and other covariates. Therefore, it is difficult to draw strong conclusions from these height studies. Of some interest is that two studies showed sex differences in the height and cognitive abilities association, providing further reason to examine effect modification by sex in height growth studies.

The height growth studies have several strengths. The repeated height growth and varied cognitive construct measures allowed for a substantial number of analyses, the results of which form a detailed picture of the relationship during child development, especially from birth through mid-childhood. The repeated measures also allowed for analyses of growth trajectories in relation to cognitive abilities. Analyses were well powered, in many cases finding small but statistically significant relationships between exposure and outcome variables. Most analyses were based on birth cohort data and included many, if not all, important covariates measured around birth and in early childhood. These complex analyses were facilitated by multiple regression analyses that can accommodate several covariates. One study also used structured equation modeling which provided greater insight into the direct and indirect effects of specific variables on the outcome.[22]

A central weakness of these studies is that effect modifications by sex and SGA were not evaluated except in the Yang study which found that p values for effect modifications by sex were > 0.10 in all analyses with the outcome measured at age 6.5 years.[36] The other studies controlled for sex as a covariate in the analyses and did not report the regression coefficients of the sex variable. No studies reported on effect modification by SGA status.

Most of the studies had significant loss to follow up by the time that the outcome variables were measured and also reported differences between those lost to follow up and those retained. In addition, the sample populations in all but one of the studies were located in

Britain and Helsinki, Finland. Because of the factors, generalization of this body of results should thus be interpreted with some caution despite their overall consistency.

The positive relationships between some but not all specific height growth periods and cognitive abilities suggest that there are critical periods of cognitive development. The height growth periods analyzed in this study were dependent on available data collected for birth cohorts and these likely overlap but do not exactly match any critical periods that may exist. Therefore, the relationships between specific height growth periods and cognitive abilities may be underestimated.

Some studies mentioned biological mechanisms that may underlie the relationship between height growth and cognitive abilities. The knowledge base on brain development, including brain functions related to cognitive ability, has been growing rapidly in recent decades. The next steps in analyzing the relationships between height growth and cognitive ability should include some of these periods recognizing that available data most likely will not match up exactly with the hypothesized critical periods. This would be a useful means to test whether or not biological and epidemiological findings are consistent.

This second paper of this dissertation aims to fill some gaps in our knowledge of the association between early childhood height growth and cognitive abilities. I will examine the association between early childhood height growth and four aspects of working memory ability in middle-aged adults. This research will add to the existing body of knowledge in several ways. First, there have been no studies on working memory

outcomes in adults of any age. Second, this focus on a specific cognitive ability may be crucial to the identification of critical periods of brain development as it becomes clearer that brain areas and circuits mature at different times. Third, this will be the first study to examine associations between early childhood growth and cognitive ability in middle-aged adults. Finally, this study will examine effect modification by sex and by SGA status.

Associations Between Early Childhood Height Growth

and Adult Working Memory

Abstract

Background. Epidemiologic research suggests that height growth in specific age ranges is positively associated with subsequent cognitive abilities. We hypothesized that early childhood height growth is positively associated with adult working memory abilities. We tested this hypothesis using data from the Early Determinants of Adult Health (EDAH) study and its sister study Fetal Antecedents of Major Depression and Cardiovascular Disease (MDCVD). These studies were adult follow-up studies of two birth cohorts from the 1960's: the Child Health and Development Studies (CHDS) and New England Family Study (NEFS); both followed subjects from birth through childhood. We also examined whether the associations were modified by sex or small for gestational age (SGA) status. ***Methods.*** We recruited 227 and 247 subjects from sibling sets in the CHDS and NEFS, respectively. Almost all subjects were from same-sex sibling sets. We measured height growth as height percentile change (HPC) over three periods: birth to 4 months, 4 months to 1 year, and 1 to 4 years. Working memory was assessed by standardized tests measuring verbal recall, attention with interference, attention and processing speed. We analyzed associations between HPC and working memory test scores using mixed models to account for family correlations. Data were analyzed separately by birth cohort. ***Results.*** In the CHDS subjects, we found positive associations between HPC from 4 months to 1 year

and attention with interference, and between HPC from 1 to 4 years and verbal recall. In NEFS subjects, we found a positive association between HPC from 4 months to 1 year and processing speed. We also found inverse associations between HPC from birth to age 4 months and the attention score in subjects from the CHDS cohort as well as the verbal recall score in subjects from the NEFS cohort. Effect modification by sex was present in the associations of HPC from 4 months to 1 year with the processing speed score in subjects from the CHDS cohort and the verbal recall score in subjects from the NEFS cohort. In these associations, working memory outcomes in adult males appear to be more sensitive to early childhood growth in this period. In subjects from the CHDS cohort, female processing speed scores increased with HPC increases while male scores showed no relationship with this outcome. In subjects from the NEFS cohort, male verbal recall scores increased with HPC increases while scores for females showed no relationship with this outcome. ***Conclusions.*** These results provide some support for the hypothesis that early childhood height growth is positively associated with adult working memory ability. The association patterns across the three HPC intervals provide some evidence of critical periods of brain development with respect to working memory outcomes. Evidence of effect modification by sex in the height growth period from age 4 months to 1 year may indicate that adult working memory in males is more sensitive to development during this period.

Introduction

Epidemiological studies strongly suggest positive associations between attained height and cognitive abilities at several points during the life course.[34,35,44-52] In addition, a small group of longitudinal epidemiological studies provide limited evidence of a positive relationship between early childhood height growth and cognitive abilities in both children and adults.[22,29,36,38-40] These results are consistent with neuroscience findings that both brain development and height growth are rapid during early childhood and highly dependent on IGF-1 levels.[1-3] In fact, height growth has even been suggested as an indication of overall developmental progress, including brain development.[53,54]

Several of these epidemiological studies also indicate that associations between height growth and cognitive abilities are limited to specific growth periods and outcomes. For instance, positive relationships reported between height growth and cognitive ability outcomes in adulthood are limited to early childhood and later adolescent height growth periods.[39,40] These results while limited thus far are consistent with neuroscience findings that various cognitive abilities develop on different trajectories and originate in different developmental periods.[55]

With this emerging complex understanding of developmental timing of cognitive abilities, the existing body of research on height growth and adult cognitive ability is incomplete. Specifically, it is limited in terms of examining successive growth periods, adult outcomes and specific aspects of intelligence. Outcomes in middle age adults are of particular

interest as they represent the time of midlife transition of cognitive ability. Significant relationships between height growth and adult cognitive ability may contribute to our understanding of brain development and adult outcomes.

One cognitive ability that may be positively associated with height growth is working memory, an active system of the brain that holds information temporarily and uses that information to achieve a goal.[56] Working memory activity is centered in the prefrontal cortex of the brain, an area that matures steadily over the first two decades of life.[57] Other brain areas are also involved in working memory such as the parietal cortex and thalamus.[58,59] During infancy and early childhood, working memory ability differs between individuals, indicating differences in brain developmental timing or growth at early ages.[60] Whether these trajectories have any permanent relationship with adult working memory is unknown.

We examined the relationship between early childhood height growth and lifetime MDD with data from the Early Determinants of Adult Health Study (EDAH) and its extension, Fetal Antecedents of Major Depression and Cardiovascular Disease (MDCVD) that assessed cognitive outcomes in adults with a mean age of 44 years. The EDAH study was a follow up of selected subjects from the Child Health and Development Studies (CHDS) and New England Family Study (NEFS) birth cohorts. The MDCVD extension is a follow up of additional subjects from the NEFS. Repeated height measures were available for these cohorts and allowed us to examine the growth periods of birth to 4 months, 4 months to 1 year and 1 to 4 years. The cognitive assessment included four tests that measure specific

aspects of working memory: verbal recall, attention with interference, attention, and processing speed.   The cohort datasets also include a rich set of maternal, socioeconomic and demographic factors in early life and adulthood.

Based on research to date, we hypothesize a positive association between early childhood height growth and working memory outcomes. We also examined, in exploratory analyses, whether sex and/or small for gestational age (SGA) status were effect modifiers for the associations between height growth in specific periods and working memory outcomes. Females have different working memory skills than males[61-64] and brain development varies between males and females.[63] SGA children often have rapid catch up growth from birth to age two years and different developmental patterns as a result.[65-67]

Methods

Sample ascertainment

The data for these analyses were collected from participants in the CHDS and NEFS birth cohorts who were later followed up in adulthood as part of the EDAH or MDCVD studies. [68] Data were analyzed separately by birth cohort.

The NEFS birth cohort is comprised of the Boston, MA and Providence, RI cohorts of the multisite Collaborative Perinatal Project (CPP).   The NEFS enrolled 16,557 pregnancies between 1959 and 1965.   The study purpose was to examine antecedents of pediatric, neurological and psychological disorders in children.   The study followed up with 88% of the survivors at age 1 year and 79% at age 7 years.[69]

The CHDS study enrolled 20,530 pregnancies from the Kaiser Foundation Health Plan in the Oakland, California area between 1959 and 1966. The study purpose was to investigate events of pregnancy, labor and delivery and subsequent childhood development.[70] [71] The study remained in contact with 99.8% of the participants at age 1 and 89.4% at age 5.[71]

The EDAH study recruited same-sex sibling sets from the NEFS and CHDS cohorts. Eligible sibling sets included those where two or more same-sex siblings were discordant on birth weight for gestational age. In NEFS, the low birth weight proband was below the 20th percentile of the sex-specific birth weight for gestational age distribution and the higher birth weight sibling was at or above the 20th percentile and at least 10 percentile points higher than their sibling. These criteria were also used to select approximately half of the CHDS sibling sets; the remainder included sibling sets in which the siblings differed by at least 10 percentile points on the birth weight for gestational age distribution, but where the lower birth weight sibling was not in the lowest quintile for gestational age distribution. Further, both siblings had to be between 38 and 43 weeks completed gestation, have serum samples collected during pregnancy and growth data collected during early childhood follow up. Subjects had to live within commuting distance of the EDAH clinics. All subjects that met this criterium were eligible for enrollment. In the CHDS, 651 subjects were eligible and in the NEFS, 515 subjects were eligible. [70]

Of the EDAH-eligible subjects, 70.5% of the CHDS subjects and 61.0% of the NEFS subjects were targeted for enrollment. Resource restrictions limited recruitment efforts but selection was not differential to subject characteristics. Of these, 243 CHDS subjects and

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149 NEFS subjects were successfully recruited and assessed. These 392 subjects formed the core EDAH cohort[70] (Supplemental Figure 1).

In the NEFS for the MDCVD study, we extended the size of the cohort and included same-sex sibling sets discordant on maternal preeclampsia status (Supplemental Figure 2). These sibling pairs were, as above, required to be between 38 and 43 completed weeks of gestation.[68] We identified 644 additional subjects and 371 (57.6 %) were eligible for the adult follow up. Of these eligible subjects, 252 (67.9%) were located and 146 (57.9%) were recruited and assessed.[72]

In the combined MDCVD and EDAH samples there were 295 subjects from the NEFS cohort: 146 subjects from MDCVD and 149 subjects from EDAH. With 243 subjects from the CHDS, the combined sample size is 538 subjects (Supplemental Figure 3) [72]

From this combined sample, we excluded subjects with a history of bipolar or psychotic disorders (15 from the NEFS and 4 from the CHDS). We also excluded those with no cognitive assessments and/or incomplete data on relevant covariates. With these restrictions, we studied a total of 474 subjects: 247 from the NEFS and 227 from the CHDS. (Figure 1) There are 213 males, 108 of whom are in same-sex sibling sets. There are 261 females, 174 of whom are in same-sex sibling sets. 20 subjects were from mixed-sex sibling sets. The remaining subjects were part of sibling sets in the birth cohorts but their sibling(s) did not enroll in either the EDAH or MDCVD study. [68]

For this analysis, the study population was further reduced because of missing data for height measures in early childhood, working memory measures and covariate information. Depending on the height growth period, the number of subjects in the CHDS analyses ranged from 139 to 166. In the NEFS analyses the number of subjects ranged from 189 to 193. (Supplemental Table 1)

EDAH and MDCVD Outcome Assessments

The Institutional Review Boards at Columbia University and other participating institutions and clinics approved EDAH and MDCVD assessment procedures. All assessments were performed during a clinic visit that lasted approximately 4–5 hours. During the visit a questionnaire was administered to males on social and demographic characteristics and health history; a similar questionnaire was administered to females as part of a computer-assisted telephone interview.   Neuropsychological tests were administered, followed by a structured clinical psychiatric interview (the Structured Clinical Interview for DSM-IV). Study personnel were carefully trained and quality control measures were implemented for assessments. [70] All test scores were reviewed by Jill Goldstein, PhD at Brigham and Women's Hospital in Boston and Jo-Ann Donatelli, PhD at Brown University.[68]

The neuropsychological test battery included four tests that measure aspects of working memory. Scores on each of these tests were analyzed in relationship to percentile height change in this study.

A modification of the California Verbal Learning Test (CVLT)[73] was used to assess verbal

recall. Sixteen words were read to the subject at 1-second intervals and then the subject recalled as many of the words as possible. The test is typically administered five times but due to time limitations, only three administrations were performed. The total number of correct recalled words in all three trials is the total recall score.

The Seidman Continuous Performance Test (CPT)[74] was used to test attention and attention with interference. The subject listens to a series of letters read aloud then taps a pencil on a desk when they hear certain patterns. To test attention, subjects tap upon hearing the letter 'Q' when immediately preceded by letter 'A'. To test attention with interference, subjects tap upon hearing a 'Q' four letters after hearing an 'A'. This latter test also has an interference component as an additional distracter. Scores are defined as the number of omission errors. The attention with interference score is the total number of omissions in three trials and attention score as the total number of omissions in two trials.[74]

The Wechsler Adult Intelligence Scale Digit Symbol Test[75] was used to evaluate processing speed and subtle brain dysfunction. The subject encodes a series of letters with symbols using a key provided with the test. The subject has 90 seconds to complete the test. The number of items correct is the raw score, which is then converted to an age-adjusted standard score.

Height Growth

Height and Height Growth Measure. The measure of a study subject's height relative to others in the cohort was the height percentile. Height percentiles for the subjects from the CHDS and NEFS cohorts were assigned from height percentiles indices for these source birth cohorts. These indices consisted of height percentiles for birth, ages 4 months, 1 year and 4 years. The methodology of calculating height percentiles was complex and is described in more detail in the next section.

The measure of a subject's height growth in this study is the height percentile change ('HPC') for a given HPC interval. This is calculated by subtraction of the subject's height percentile at the beginning of the period from that at the end of the period. HPC was calculated for the growth periods between birth and age 4 months, ages 4 months and 1 year and ages 1 to 4 years.

Calculation of the Height Percentiles and the Indices. Since indices were calculated separately by sex, cohort, and gestational week (38 to 43 weeks) 24 indices were calculated. The sizes of these cohort groups are set forth in Section 1 of the Methodology Appendix. The subjects in these groups are referred to as cohort subjects.

We used smoothing spline methods[76] to construct height growth curves from birth to age 4 years for each cohort subject. This was necessary in order to obtain imputed measures of

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height at exactly ages 4 months, 1 year and 4 years. For most of the cohort subjects, height was measured in periods surrounding these age points, not exactly at one of these ages. This method calculates growth curves informed by the cohort subject's height data and by the growth trend for the cohort as a whole.

We excluded inaccurate data points from the smoothing spline calculations. We deleted the small number of observations that were implausible; for example, a recorded height of 72 inches at age 1 year was indicated for one subject. The number of implausible observations was 9 in the CHDS cohort and 20 In the NEFS cohort. We also deleted observations that indicated negative height growth. (N = 110 in the CHDS cohort (out of over 14,000) and N = 156 (out of over 12,000) in the NEFS cohort) had height measures indicating negative height growth during one or more growth periods. In this situation, height measurements at the beginning and end of the negative growth period were deleted.

Smoothing splines were calculated using R (see Section 2 of the Methodology Appendix). This method requires a least three data points per cohort subject to estimate individual growth curves in this analysis. Because of missing data it was not possible to calculate growth curves for 54 subjects from the NEFS cohort and 24 subjects from the CHDS cohort.

We calculated distributions of height for each of the four age points from the smoothing spline results. We normalized the height distributions using a Box & Cox transformation.

The power parameter λ in the Box-Cox transformation was allowed to vary by group. [77] The resulting z scores were calculated from these normalized distributions. The corresponding height percentiles were calculated with a nonparametric ranking procedure. There were 24 separate indices based on cohort, sex and gestation week. (Further details on the Box Cox transformation, standardization of the variables and calculation of the index height percentiles are set forth in Section 3 of the Methodology Appendix.)

For the study subjects, height percentiles were assigned from the indices according to birth cohort, sex and gestation week. These were then collated and added to the study dataset. We deleted imputed study subject height measures if they were taken outside windows of time around the age points or if there was no measurement taken for the age point (i.e., it was imputed by the smoothing spline method based on three other height measures) for a subject. These windows were 70 days (480 days total) at 4 months, 240 days (480 days total) at 1 year and 360 days (720 days total) at 4 years. In total, this resulted in the deletion of 6 height measures in the CHDS and 1 in the NEFS.

Statistical Methods

Summary statistics were calculated for exposure and outcome variables and for other sample characteristics such as sex, race and maternal education. This includes the estimated height imputed from the spline methodology and the corresponding height percentiles. We used SAS Version 9.3 for all analyses.

Generalized linear mixed models were used to examine relationships between HPC and the adult working memory outcome measurements. For continuous outcomes including verbal recall, attention with interference and processing speed scores, linear mixed models with identity link were used while for the dichotomized attention score (cut point score = 18), logistic regression models with generalized estimating equations were used. The models accounted for within family correlations. (For further details on the models and corresponding SAS code, see section 4 of the Methods Appendix).

For each pair of an HPC and a working memory score outcome, we estimated three models, progressively adjusting for controlling variables. First, we estimated an unadjusted model using HPC as the exposure variable and scores from a single working memory test as the outcome. Next we estimated a model adjusted for sex and the height percentile at the beginning of the relevant HPC interval. Finally we estimated a model further adjusting for maternal variables (age, height, parity, maternal smoking), SES (maternal education) and subject-related variables (birth order, race and age at follow-up interview). We also repeated the fully adjusted modeling described above, replacing the continuous HPC variable by tertiles.

We assessed effect modification by sex and SGA status using these mixed models. SGA status was defined as birth weight for gestational age in the lowest 10% of the distribution for the underlying cohort (CHDS or NEFS). We analyzed effect modification by sex with stratified analyses in the fully adjusted models described above. The Wald test statistic was used to determine the significance of sex differences. This methodology was not feasible for

the evaluation of effect modification by SGA status because only a small number of subjects were SGA. Therefore, we added an interaction term (SGA*HPC) to the fully adjusted models to test for effect modification.

The proportion of missing covariates ranged from 3% to 4% in the CHDS analyses and from 25% to 29% in the NEFS analyses. (See Supplemental table 2). Missing maternal height information accounts for most of the missing data in the NEFS cohort. We used multiple imputation[78] to estimate missing maternal height data as well as all missing covariate data in each analysis of NEFS subjects. For each imputation, we used the exposure variable, outcome variable, all covariates and other variables correlated to the maternal height variable as the basis of the calculations. This information was used to generate 20 imputations per missing observation. The imputed covariates were used in all of the generalized linear models. (Further details on imputation methods and SAS code can be found in Section 5 of the Methodology Appendix.)

Results

Descriptive Statistics

Subjects from the CHDS and NEFS cohorts differ markedly in outcome and covariate measures. Demographic characteristics are presented in Table 3 and height growth and working memory measures for both groups are presented in Table 4. In comparison with the NEFS subjects, CHDS subjects were more likely to be non-white and their mothers were older, less educated and less likely to have been smokers around the time of birth. CHDS

subjects had consistently higher mean scores on each of the working memory tests compared to NEFS subjects. Mean scores for the California Verbal Learning Test and the WAIS Digit Symbol Test are in the expected range.[79,80] There are no normative studies for the Seidman CPT Test but the scores in this study appear to be in line with scores on other studies of adults. (private communication, Larry J Seidman PhD)

The two birth cohorts also had differing demographic characteristics in adulthood. CHDS subjects had height mean annual household income than NEFS subjects ($66,800 versus $59,000). The CHDS subjects also have a higher level of high school graduation than NEFS subjects (79.0% versus 72.2%).

Subjects from the CHDS cohort were larger than NEFS subjects in terms of both birth length and birth weight with an equivalent gestational age. At age 4 years, mean estimated height for CHDS subjects was over 1 inch greater than for NEFS subjects.

Regression Results

The fully adjusted analyses are discussed by outcome below. (Tables 5a and 5b)

Verbal recall. In the CHDS group, we found that for a 10-point increase in HPC from ages 1 to 4 years the verbal recall score increased 0.47 points (0.08 standard deviation (sd) units, p=0.11). In the NEFS group, for a 10-point increase in HPC from birth to age 4 months, the mean verbal recall score decreased 0.29 points (0.05 sd units, p = 0.07).

Attention with Interference. In the CHDS cohort, we found that for a 10-point increase in HPC from ages 4 months to 1 year the mean attention with interference score increased 0.61 points (0.18 sd units, p = 0.002). In the NEFS, there was no evidence of an association between HPC in any interval and the attention with interference score.

Attention. In the CHDS cohort, the OR of an attention score of 18 compared to a lower score was 0.85 (95% CI 0.71, 1.02) for a 10-point increase in HPC from birth to age 4 months. In the NEFS cohort there is no evidence of an association between HPC in any interval and the attention score.

Processing Speed. In the CHDS, there were no associations found between HPC in any interval and the processing speed score. In the NEFS group, for a 10-point increase in HPC from ages 4 months to 1 year, the processing speed score increased 0.14 points (0.05 sd units, p = 0.10).

We also analyzed the data from the NEFS cohort without using multiple imputation and the results were similar. (Supplemental Table 3) These main results, including the imputed data for the NEFS cohort, were generally confirmed in analyses of associations between tertiles of HPC and working memory outcomes (Supplemental Table 3).

There was evidence of effect modification by sex in analyses of associations between HPC from ages 4 months to 1 year and two working memory outcomes: the processing speed

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score in the CHDS group (p = 0.03) and the verbal recall score in the NEFS group (p = 0.02) (Table 6). In both of these analyses, for an equivalent increase in HPC, male test scores increased while female test scores decreased slightly. Effect modification by sex was also suggested in the relationship between HPC from ages 1 to 4 years and the attention score in the NEFS cohort (p = 0.09) where the direction of the association was inverse in females and positive in males.

Despite limited statistical power in the sex-stratified analyses, there were some notable patterns in the results and additional associations that were not found in the main analyses. In the associations between HPC from birth to age 4 months and working memory scores, the effect magnitude was somewhat higher in females. For example, in the CHDS analysis of HPC from birth to age 4 months, the estimated beta (sd) for the association with the processing speed score was 0.23 (0.15) in females versus -0.01 (0.16) in males. In the CHDS, this was found in associations with all working memory outcomes. In the NEFS group, this was found in associations with the verbal recall, attention with interference and processing speed outcomes.

 In the associations between HPC from 4 months to 1 year and working memory outcomes, the effect magnitude was higher in males for most of the analyses. In the CHDS group, this was found for all working memory outcomes. In the NEFS group, this was found for verbal recall and attention outcomes.

The sex-stratified analyses also revealed some associations in females that were not apparent in the main analyses. In the CHDS group, for a 10-point increase in HPC from ages 1 to 4 years, the processing speed score increased 0.47 points (0.15 sd units, p = 0.01). In the NEFS cohort, we found two additional associations. For a 10-point increase in HPC from birth to age 4 months, the verbal recall score decreased 0.54 points (0.09 sd units, p = 0.02). For a 10-point increase in HPC from birth to age 4 months, the processing speed score declined 0.18 points (0.06 sd units, p = 0.08).

There was no evidence of effect modification by SGA status (Supplemental tables 4a and 4b).

Adjustment for birth weight, used in the selection of the sample, did not meaningfully change the results (Supplemental Table 5).

Discussion

This is the first study to evaluate the association between early childhood height growth and adult working memory ability. This study is unique because the hypotheses were evaluated in two cohorts with different socio-demographic characteristics at birth, but with identical measures of adult circumstances and working memory.

We found several associations supporting our hypothesis that early childhood height growth is positively associated with adult working memory   In the CHDS subjects, there were positive associations between HPC from 4 months to 1 year and attention with

interference, and between HPC from 1 to 4 years and verbal recall. In NEFS subjects, there was a positive association between HPC from 4 months to 1 year and processing speed. We also found a few inverse associations between HPC from birth to age 4 months and the attention score in subjects from the CHDS cohort as well as the verbal recall score in subjects from the NEFS cohort. Despite limited statistical power, the sex-stratified analyses largely confirmed these positive and inverse associations in one or both of the sexes. In addition we found a few associations that were only apparent in females.

The association patterns across the three HPC intervals for a specific working memory outcome provide some evidence of critical periods of brain development with respect to cognitive ability outcomes. In the main analyses of both cohorts, associations are found in only one HPC interval for a specific outcome. For example, in analyses of HPC and the attention with interference score, an association was only found for the HPC interval from 4 months to 1 year. This pattern is also observed in the analyses stratified by sex.

Our finding of effect modification by sex and the higher magnitude of effects in males for the HPC interval from 4 months to 1 year may indicate that adult working memory abilities in males are especially sensitive to development during this interval. These results for males are more consistent between cohorts in this HPC interval than in any of the other analyses perhaps indicating the strength of the effect in this period.

This effect modification result is consistent recent with neurodevelopment research on brain network development. Gao explored changes in connectivity in network formation and between networks from birth to age 2 years using resting state fMRI technology. He found that the rate of connectivity growth between the left and right frontoparietal networks was higher in males.[81] The frontoparietal networks are highly associated with working memory functions.[82-84] . It is interesting to note that Gao did not find sex differences in any other network analyses.

While there were no findings of effect modification by SGA status, it should be noted that this result could be due to Type II error, as there were a small number of subjects with SGA.

The inverse associations we found in the HPC intervals from birth to age 4 months year are interesting but the small sample size precludes further analysis.

The results were not consistent between subjects from the CHDS and NEFS cohorts. In many instances, the directions of the associations were opposite. In the stratified analyses, this inconsistency was more pronounced for females while the analyses of males were more consistent. There are possible explanations for these inconsistent results. First, subjects from these cohorts differed in terms of the distributions of race, socioeconomic status and other variables as described above. Second, there may be unmeasured confounders or contextual differences that account for the differences. Third, these differences could reflect that findings are due to chance.

This study had several strengths compared to previous research. First, we collected the study sample from two birth cohorts with extensive measures of childhood height and relevant covariates relating to both the subjects and their mothers. These characteristics allowed us to examine several early childhood growth periods and to adjust the analysis for a wide range of potential confounder variables. Second, we collected extensive cognitive measures on adult subjects and have four measures that capture different aspects of working memory, allowing for a rich evaluation of this cognitive ability. Third, as already noted, we were able to analyze two significantly different cohorts with virtually identical data available for analysis.

There are some study weaknesses. First, many study subjects are missing height measures at different age points. The missing data problem is compounded since the exposure variable, HPC, requires two consecutive height measurements. The result is lower statistical power than expected. Multiple comparisons are an issue in this study given the high number of analyses.

These study results provide limited evidence for a positive association between early childhood height growth and adult working memory ability. They also provided evidence that relationships differ by sex; perhaps indicating that adult working memory ability is sensitive to different periods of brain development by sex. These findings must be interpreted cautiously due to unexplained findings of many inverse associations inconsistencies between the cohorts.

Associations Between Early Childhood Height Growth

and Lifetime Major Depressive Disorder in Adults

Abstract

Background. Early childhood height growth has been positively associated with cognitive function across the life course. This association may be one indication that height growth and neurodevelopment are correlated in early childhood. Whether height and height growth are related to psychiatric outcomes over the life course is unknown. We hypothesized that early childhood height growth is inversely associated with lifetime major depressive disorder (lifetime MDD) in adults. We tested this hypothesis in two follow up studies of birth cohorts (the Child Health and Development Studies (CHDS) and the New England Family Study (NEFS)) from the 1960s and assessed in middle age. ***Methods.*** We measured height growth as height percentile change (HPC) over specific growth periods. Lifetime MDD was assessed at a mean age of 44 years using modules from the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV version. We analyzed associations between HPC and lifetime MDD in three growth periods: birth to 4 months, 4 months to 1 year, and 1 to 4 years. Cohorts were analyzed separately (i.e. CHDS and NEFS). Mixed logistic models were used to account for inter-sibling correlations. ***Results.*** We found no associations between HPC and lifetime MDD in most analyses. In the CHDS, the ORs for lifetime MDD given a 10 point increase in HPC for the three periods were: 0.98 (95% CI 0.82, 1.17) for birth to 4 months, 1.00 (95% CI 0.79, 1.26) for 4 months to 1 year, 0.99 (95% CI 0.81, 1.20) for 1 to 4 years. In the NEFS, the ORs for lifetime MDD given a 10 point increase in HPC for the three periods were: 0.97 (95% CI 0.86, 1.09)

for birth to 4 months, 0.96 (95%CI 0.82, 1.12) for 4 months to 1 year, and 0.94 (95% CI 0.80, 1.10) for 1 to 4 years. ***Conclusions***. Results do not support the association between early childhood height growth and lifetime MDD. However, the effect modification by sex and SGA status should be examined further.

Introduction

Early childhood height growth has been positively associated with cognitive function across the life course.[22,29,36,39,40] This association may be one indication that height growth and neurodevelopment are correlated in early childhood, consistent with neuroscience findings that both brain development and height growth are highly dependent on IGF-1 levels.[1-3] Whether early childhood height growth is also associated with neuropsychiatric outcomes is a topic that has received little attention.

We hypothesized that early childhood height growth is inversely associated with lifetime MDD in adults. We used data from the Early Determinants of Adult Health (EDAH) study and its extension, Fetal Antecedents of Major Depression and Cardiovascular Disease (MDCVD) to test this hypothesis. This study included assessments of neuropsychiatric outcomes in adults with a mean age of 44 years. The EDAH study was a follow up of selected subjects from the Child Health and Development Studies (CHDS) and the New England Family Study (NEFS) birth cohorts. The MDCVD extension is a follow up of additional selected subjects from the NEFS.[70] Repeated height measures were available for these cohorts and allowed us to examine the growth periods of birth to 4 months, 4 months to 1 year and 1 to 4 years. The psychiatric assessment, including lifetime MDD, was conducted by clinical professionals using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV.[72] The cohort data also include extensive data on maternal, socioeconomic and demographic factors in early life and adulthood.

In addition to the hypothesis, we also explored whether sex and/or small for gestational age (SGA) status were effects modifiers for associations between height growth and lifetime MDD. Females have higher prevalence of MDD than males[85] and brain development varies between males and females.[63] SGA children often have rapid catch up growth from birth to age two years and different development patterns as a result. [65-67]

Methods

Sample ascertainment

The data for these analyses were collected from participants in the CHDS and NEFS birth cohorts who were later followed up in adulthood as part of the EDAH and MDCVD studies. Data were analyzed separately by birth cohort.

The NEFS birth cohort is comprised of the Boston, MA and Providence, RI cohorts of the multisite Collaborative Perinatal Project (CPP). The NEFS enrolled 16,557 pregnancies between 1959 and 1965. The study purpose was to examine antecedents of pediatric, neurological and psychological disorders in children. The study followed up with 88% of the survivors at age 1 year and 75% at age 4 years.[69]

The CHDS study enrolled 20,530 pregnancies from the Kaiser Foundation Health Plan in the Oakland, California area between 1959 and 1966. The study purpose was to investigate events of pregnancy, labor and delivery and subsequent childhood development.[70,71] The

study remained in contact with 99.8% of the participants at age 1 and 89.4% at age 5.[71]

The EDAH study recruited same-sex sibling sets from the NEFS and CHDS. Eligible sibling sets included those where two or more same-sex siblings were discordant on birth weight adjusted for gestational age. In NEFS, the low birth weight proband was below the 20th percentile of the sex-specific birth weight for gestational age distribution and the higher birth weight sibling was at or above the 20th percentile and at least 10 percentile points higher. These criteria were also used to select approximately half of the CHDS sibling sets; the remainder included sibling sets in which the siblings differed by at least 10 percentile points on the birth weight for gestational age distribution. Further, both siblings had to be between 38 and 43 weeks completed gestation. Siblings were required to live within commuting distance of the Boston or Oakland clinics.[70]

Of the EDAH-eligible subjects, 70.5% of the CHDS subjects and 61.0% of the NEFS subjects were targeted for recruitment. Resource restrictions limited the recruitment effort but selection was not differential to subject characteristics.   Of these, 243 CHDS subjects and 149 NEFS subjects were successfully recruited and assessed. These 392 subjects formed the core EDAH cohort (Supplemental Figure 1).[70]

In the NEFS for the MDCVD study, we extended the size of the cohort and included same-sex sibling sets discordant on maternal preeclampsia status (Supplemental Figure 2). These sibling pairs were, as above, required to be between 38 and 43 completed weeks of gestation.[68] We identified 644 additional subjects and 371 (57.6 %) were eligible for the

adult follow up. Of these eligible subjects, 252 (67.9%) were located and 146 (57.9%) were

recruited and assessed.[72]

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146 subjects from the MDCVD and 149 subjects from the EDAH cohort. With 243 subjects

from the CHDS, the combined sample size is 538 subjects (Supplemental Figure 3). [72] From

this combined sample, we excluded subjects with a history of bipolar or psychotic

disorders (15 from the NEFS and 4 from the CHDS). We also excluded those with no

cognitive assessments and/or incomplete data on relevant covariates.   With these

restrictions, we studied a total of 474 subjects: 247 from the NEFS cohort and 227 from the

CHDS cohort (Figure 1). There are 213 males, 108 of whom are in same-sex sibling pairs.

There are 261 females, 174 of whom are in same-sex sibling sets.[68] 20 subjects were from

mixed sex sets. The remaining subjects were part of sibling sets in the birth cohorts but

their sibling did not enroll in either the EDAH or MDCVD study.[68]

For this analysis, the study population was further reduced due to missing data on height

measures in early childhood, the lifetime MDD outcome and covariate information as

described in the Methods sections. Depending on the height growth period the number of

subjects in the CHDS analyses ranged from 149 to 176. In the NEFS analysis, the number of

subjects ranged from 203 to 208 (Supplemental Table 6).

EDAH and MDCVD Outcome Assessments

The Institutional Review Boards at Columbia University and other participating institutions

and clinics approved EDAH and MDCVD assessment procedures. All assessments were performed during a clinic visit that lasted approximately 4–5 hours. During the visit, a questionnaire was administered to males on social and demographic characteristics and health history; a similar questionnaire had been administered to females as part of a computer-assisted telephone interview.[68]   Lifetime mood and anxiety disorders and substance use were assessed during the in-person clinic visit under the leadership of Jill Goldstein, PhD at Brigham and Women's Hospital in Boston.   Clinical interviewers administered relevant modules from the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV to assess lifetime MDD. These interviewers were trained and Dr. Goldstein's diagnostic team maintained quality control. Dr. Goldstein and the clinical coordinator reviewed all diagnostic materials. Diagnoses were assigned by consensus. A third experienced clinician reviewed the material in the infrequent case of a disagreement among the diagnostic team[72]

Height Growth

Height and Height Growth Measures. The measure of a study subject's height used in this study was the height percentile. Height percentiles for the subjects in the CHDS and NEFS groups were assigned from height percentile indices for these source birth cohorts. These indices consisted of height percentiles for birth and ages 4 months, 1 year and 4 years. The methodology of calculating height percentiles is described in more detail in the next section.

The measure of a subject's height growth in this study is the height percentile change (HPC) for a given growth period. This is calculated by subtraction of the subject's height percentile at the beginning of the period from that at the end of the period. HPC was calculated for the growth periods between birth and age 4 months, ages 4 months and 1 year and ages 1 to 4 years.

Calculation of the Height Percentile and the Indices. Since indices were calculated separately by sex, cohort and gestation week (38 to 43 weeks), 24 indices were calculated. The sizes of these cohort groups are set forth in Section 1 of the Methodology Appendix. The subjects in these groups are referred to as cohort subjects.

We used smoothing spline methods[76] to construct height growth curves from birth to age 4 years for each cohort subject. This was necessary in order to obtain imputed measures of height at exactly ages 4 months, 1 year and 4 years. For most of the cohort subjects, height was measured in periods surrounding these age points, not exactly at one of these ages. This method calculates growth curves informed by the cohort subject's height data and by the growth trend for the cohort as a whole.

We excluded inaccurate data points from the smoothing spline calculations.

We deleted the small number of observations that were implausible; for example, a recorded height of 72 inches at age 1 year was indicated for one subject. The number of implausible observations was 9 in the CHDS and 20 In the NEFS cohort. We also deleted observations that indicated negative height growth. (N = 110 (out of over 14,000) in the CHDS cohort and N = 156 (out of over 12,000) in the NEFS cohort). In this situation, height measurements at the beginning and end of the negative growth period were deleted.

Smoothing splines were calculated using R (see Section 2 of the Methodology Appendix). This method requires at least three data points per cohort subject to estimate individual growth curves in this analysis. Because of missing data it was not possible to calculate growth curves for 54 subjects from the NEFS cohort and 24 subjects from the CHDS cohorts.

We calculated distributions of height for each of the four age points from the smoothing spline results. We normalized the height distributions using a Box & Cox transformation. The power parameter λ in the Box-Cox transformation was allowed to differ by group. [77] The resulting z scores were calculated from these normalized distributions. The corresponding height percentiles were calculated with a nonparametric ranking procedure. There were 24 separate indices based on cohort, sex and gestation week. (Further details on the Box Cox transformation, standardization of the variables and calculation of the index height percentiles are set forth in Section 3 of the Methodology Appendix.)

For the study subjects, height percentiles were assigned from the indices according to birth cohort, sex and gestational week. These were then collated and added to the study dataset. We deleted imputed study subject height measures if they were taken outside windows of time around the age points or if there was no measurement taken for the age point (i.e. it was imputed by the smoothing spline method based on the other height measures for a subject). These windows were on each side of the age points and were 70 days (140 days total) at 4 months, 240 days (480 days total) at 1 year and 360 days (720 days total) at 4 years. In total, this resulted in the deletion of 6 measures in the CHDS and 1 in the NEFS.

Statistical Methods

Summary statistics were calculated for exposure and outcome variables and for other sample characteristics such as sex, race and maternal education. This includes the estimated height imputed from the spline methodology and the corresponding height percentiles. We used SAS Version 9.3 for all analyses.

Logistic regression models with generalized estimating equations were used to examine the relationship between HPC and the dichotomous lifetime MDD status outcome. Family identification was included to account for within family correlations. (For further details on the models and corresponding SAS code see Section 4 of the Methods Appendix).

For each HPC interval and a lifetime MDD outcome, we estimated three models, progressively adjusting for control variables. First, we estimated an unadjusted model using HPC as the exposure variable and lifetime MDD status as the outcome. Next, we estimated a model adjusted for sex and the height percentile at the beginning of the relevant HPC interval. Finally we estimated a model further adjusted for maternal variables (age, height, parity, maternal smoking), SES (maternal education) and subject-related variables (birth order, race and age at follow-up interview, family history of mental illness). We also repeated the fully adjusted modeling described above, replacing the continuous HPC variable by tertiles to examine nonlinear associations.

We assessed effect modification by sex and SGA status using mixed models. SGA status was defined as birth weight for gestational age in the lowest 10% of the distribution for the underlying cohort (CHDS or NEFS). We analyzed effect modification by sex with stratified analyses in the fully adjusted models described above. The Wald test statistic was used to determine the significance of sex differences. This methodology was not feasible for the evaluation of effect modification by SGA status because only a small number of subjects were SGA. Therefore, we added an interaction term (SGA*HPC) to the fully adjusted models to test for effect modification.

The proportion of missing covariates ranged from 3% to 4% in the CHDS analyses and from 25% to 29% in the NEFS analyses. (Supplemental Table 7). Missing maternal height information accounts for most of the missing data in the NEFS cohort. We used multiple imputation[86] to estimate missing maternal height data as well as all missing covariate data

in each NEFS analysis. For each imputation, we used the exposure variable, outcome variable, all covariates and other variables correlated to the maternal height variable as the basis of the imputation calculations. This information was used to generate 20 imputations per missing observation. The imputed covariates were used in all generalized linear models. (Further details on the imputations methods can be found in Section 5 of the Methodology Appendix.)

Results

Descriptive Statistics

Subjects from the CHDS and NEFS cohort differ markedly in outcome and covariate measures. Demographic characteristics are presented in Table 7 and height growth and the lifetime MDD prevalence are presented in Table 8. In comparison with NEFS subjects, CHDS subjects were more likely to be non-white and more likely to have a family history of mental illness. CHDS mothers were older, less educated and less likely to have been a smoker around the time of birth than NEFS mothers. In adulthood, CHDS subjects had higher mean annual household income than NEFS subjects ($66,800 versus $59,000). The CHDS subjects also have a higher level of high school graduation than NEFS subjects (79.0% versus 72.2%).[72] These adult results are not included in any of the tables.

The prevalence of lifetime MDD was 25% in CHDS subjects, significantly lower that the 38% prevalence level in NEFS subjects.

Subjects from the CHDS cohort were larger than NEFS subjects in terms of both birth length and birth weight with an equivalent gestational age. At age 4 years, mean estimated height for CHDS subjects was over 1 inch greater than for NEFS subjects.

Regression Results

In analyses of subjects from both the CHDS and NEFS cohorts, we found no evidence of associations between HPC in any interval and lifetime MDD (see Table 9). The odds ratios for lifetime MDD for a 10-point increase in HPC are uniformly near 1.0 and 95% confidence intervals overlap 1.0 in each analysis. These results were confirmed in analyses of associations between tertiles of HPC and lifetime MDD outcomes in each growth interval. (Supplemental Table 8) The analysis is powered to detect a minimum proportion change of 10-11%.

In subjects from the NEFS cohort, we found effect modification by sex in the association between HPC from birth to age 4 months and lifetime MDD (p=0.02). (Table 10) A 10-point increase in HPC in this period was inversely associated with lifetime MDD in males (OR = 0.74, 95% CI = 0.58, 0.97) but not in females (OR = 1.07, 95% CI = 0.90, 1.28). While we also found similar inverse associations for males in the later HPC intervals, they were attenuated and there was no evidence of effect modification by sex. In subjects from the CHDS cohort, we found no effect modification by sex.

In subjects from the CHDS cohort, we found some evidence of effect modification by SGA status for the HPC intervals from birth to age 4 months (p=0.06) and from ages 1 to four years (p=0.10). (Table 11a) For the growth period from birth to age 4 months increases in HPC were inversely associated with lifetime MDD in subjects with SGA. The effect is opposite for the interval from ages 1 to 4 years, where increases in HPC were associated with increased risk of lifetime MDD. There was no strong evidence of any association between either HPC or SGA and lifetime MDD. We found no effect modification by SGA status in subjects from the NEFS cohort. (Table 11b)

Adjustment for birth weight, used in the selection of the sample, did not meaningfully change the results (Supplemental Table 9).

Discussion

This study evaluated the association between early childhood height growth and lifetime MDD in middle age adults. This study is unique because the hypotheses were evaluated in two cohorts with very different socio-demographic characteristics at birth, but with identical measures of adult psychiatric outcomes.

We found consistently null results in the main analyses suggesting that, in general, early childhood neurodevelopment (indicated by height growth), is not on the causal pathway to lifetime MDD. However, since our study sample size could only detect a minimum effect size of 10-11%, there is low statistical power in this analysis and results are possibly explained by Type II error.

However, our effect modification analyses provide some evidence that, in certain circumstances, early childhood height growth may be associated with risk of lifetime MDD. In male subjects from the NEFS cohort, our finding that HPC increases in early postnatal months were associated with lower risk of lifetime MDD could be evidence of a critical period for male susceptibility to lifetime MDD. Our analysis shows that this protective effect may extend to later HPC intervals as the effect estimates are similar though the associations are attenuated.

In SGA subjects from the CHDS cohort, our finding that increases in HPC from birth to age 4 months were protective against lifetime MDD while increases in HPC from ages 1 to 4 years increased risk of lifetime MDD may also be evidence of critical periods effects. However, since we did not detect meaningful independent associations between HPC and SGA and lifetime MDD, it is difficult to interpret these findings.

 The inconsistencies between the cohorts for effect modification could be due to a few factors. First, statistical power is limited, especially for effect modification analyses. Second, subject characteristics differed widely between the two cohorts, as evidenced by the fact that the prevalence of lifetime MDD was 25% in subjects from the CHDS cohort and 38% in subjects from the NEFS cohort. These prevalence levels, especially for the NEFS cohort, are higher than in some population studies.[85] The cohorts varied in many other aspects as discussed in the Results section above. Third, the associations could be due to chance.

Birth weight is a crude but practical measure of fetal development and has been associated with several health outcomes including cardiovascular disease, type-2 diabetes and intelligence.[87-89] More recently, one study found that birth weight was inversely associated with adult mental disorders, including affective disorders. These associations were found across the distribution of birth weight and increased from the highest to lowest birth weight.[90] Our study examined birth length, not birth weight, and was probably too small to detect the effect sizes found in the study cited above. Nonetheless, out results may provide preliminary evidence indicating that fetal development is more important than early childhood development in terms of the risk of adult lifetime MDD.

This study had several strengths. First, we collected the study sample from two birth cohorts with extensive measures of childhood height and relevant covariates relating to both the subjects and their mothers. These characteristics allowed us to examine several early childhood growth periods and to adjust the analysis for a wide range of potential confounder variables. Second, as already noted, we were able to analyze two significantly different cohorts with virtually identical data available for analysis. We are more confident of the results since they are consistent between the cohorts. However, our confidence is tempered somewhat by the inconsistent findings in the sex-stratified analysis. Third, we used the Structured Clinical Interview for diagnosis to assess lifetime MDD using trained clinicians which is a strong measure of lifetime MDD and more accurate than self-reported measures.

There are study weaknesses. First, many study subjects are missing height measures at different age points. The missing data problem is compounded since the exposure variable, HPC, requires two consecutive height measurements. The result is lower statistical power than expected though the results are consistently and strongly null.

The main results of our study do not support an association between early childhood height growth and risk of lifetime MDD. However, the effect modification by sex and by SGA results are interesting and should be examined in analyses with sufficient statistical power. While the effect modification analyses provide some evidence that early childhood height growth is associated with lifetime MDD in males and SGA subjects, these findings must be interpreted cautiously due to inconsistencies between the cohorts.

Summary, Special Considerations and Next Steps

Summary

Adult cognitive deficits and psychiatric disorders adversely impact quality of life and productivity of those affected, their family, friends and colleagues as well as the state of society in general. To date, life course research has helped identify prenatal and early life exposures and experiences that can have lasting affects on adult health but this research has been limited in terms of adult neurodevelopmental outcomes.

The purpose of my dissertation was to add to the knowledge concerning early life growth and adult neurodevelopmental outcomes. More specifically, I evaluated whether early childhood height growth (birth to age four years), as an indicator of overall early development, is associated with working memory abilities and lifetime major depressive disorder in middle-age adults. This question has important implications for our understanding of the developmental origins of cognitive ability and of major depressive disorder. It may have policy implications related to child nutrition, a factor closely related to suboptimal height growth (stunting) and development, found mainly in developing countries.[91]

In Chapter 1, I prepared a systematic review of the epidemiological literature on the association between height growth and cognitive abilities across the life course. The purpose of the review was to evaluate the existing body of knowledge on associations

between height growth and cognitive abilities and to identify areas appropriate for further research. The review concluded that the evidence that height growth in several periods of early childhood are associated with varied measures of intelligence although the body of research is limited. This review also identified research gaps. There were no studies of early childhood height growth and cognitive outcomes in middle age adults. Most study outcomes were general measures of cognitive ability such as total IQ or major subsets such as verbal IQ or performance IQ.

In Chapter 2, I used data from the EDAH study, and corresponding birth cohorts, to analyze associations between early childhood height growth and working memory ability. I examined three growth periods: birth to 4 months, 4 months to 1 year and 1 to 4 years. Cognitive tests were used to measure four aspects of working memory: verbal recall, attention with interference, attention and processing speed. I found positive associations in both birth cohorts and the pattern of results suggested critical period effects in each of the three periods noted above. However, these main analysis results were not consistent by cohort perhaps due to unmeasured cohort differences. I found effect modification by sex in both cohorts with positive associations between height growth and adult working memory ability in males only from age 4 months to 1 year.

In Chapter 3, I used data from the EDAH study, and corresponding birth cohorts, to ascertain whether an association exists between early childhood height growth and lifetime MDD. I did not find any association between early childhood height growth in any period and lifetime MDD in the main analysis in either cohort. There was some evidence of

an inverse association between height growth from birth to age 4 months and lifetime MDD in males in the NEFS cohort. In the CHDS cohort, there was some suggestive evidence of an inverse association between height growth from birth to 4 months and lifetime MDD for SGA subjects, and a positive association between height growth from 1 to 4 years and lifetime MDD in the SGA subjects.

The ability to analyze the same research questions in two cohorts is a key strength of this dissertation. Replication of results in an unrelated population can strengthen causal inference and this was found in the main lifetime MDD analysis and in the sex-stratified analysis of males in the working memory study. A failure to replicate results may indicate that the findings are due to chance or that there are other differences between the cohorts that account for the inconsistent results, as discussed below. This was observed in the main analyses of the working memory study and in the effect modification by sex analysis in the depression study.

Special Considerations

There are several aspects of this study that must be noted given their importance to analysis and inference. First, EDAH and MDCVD selection criteria provided that many subjects with low birth weight for gestational age were included as well as many subjects exposed to preeclampsia. In addition, other selections were made in the sample for this study due to missing information on height or cognitive outcomes. These steps likely resulted in selection bias that may limit the generalizability of the results.

Second, maternal education levels were used as the measure of SES in this study. Other measures are commonly used including maternal job level, family income, paternal education or paternal job level though not all of these were included in the study dataset. Adding another variable such as family income may have improved the measure of SES. However, the extent of improvement is questionable since the two variables are typically correlated and statistical power would have declined by adding another variable. The two variables could have been combined in an index, but it is not clear how each variable should be weighted. Thus we thought it optimal to include only the maternal education variable.

Third, we included attained maternal height as a covariate in this study as it is associated with cognitive outcomes. However, it is unknown whether maternal height is associated with the rate and timing of height growth during an offspring's development. Our analysis did not indicate that maternal height adjustment had a meaningful impact on results.

Fourth, there is a question of whether or not one or more measures of working memory could have been combined in a type of factor or principal components analysis. However, this approach is not suitable for this study. As noted in the earlier chapters, we suspect that development of specific brain functions may occur during different periods. Working memory is considered to be a network of brain functions and these functions may develop at different times. Therefore combining them may miss obscure important relationships.

Fifth, data from both cohorts could be combined for analysis and this would increase statistical power, an issue in the study. However, there are serious concerns about this approach. First, the many demographic differences and the inconsistent results between these cohorts suggest important unmeasured differences. Combining the cohort data may further obfuscate any existing relationships. In addition, height percentiles were calculated from the source populations at the relevant ages. If the cohorts were combined, a more standard height percentile index would need to be used. These charts date back only to the late 1970's in the United States and therefore would not be nearly as suitable as the cohort based measures.

Finally, we classified any subject in the lowest 10% of birth weight for gestational age as having a positive SGA status. While this level is typical for SGA classification, we could have used a cutoff of 20% to 25%.   We did a sensitivity analysis on the results using the continuous variable birth weight for gestational age and the results did not change in any meaningful way.

Next Steps

In addition to addressing certain gaps in the literature, this dissertation created new questions about the associations between early childhood growth and both working memory and depression outcomes in middle-age adults. As noted above, study results by cohort were inconsistent in some cases. The inconsistent results in both studies may be due to chance findings, but the number and magnitude of discrepancies suggest other

underlying reasons. There may be unmeasured contextual differences between the cohorts, or there may be specific characteristics that differ by cohort later in development or adulthood that account for the varying results. Further evaluation of these characteristics may help to clarify these questions.

The exploratory effect modification analyses in both the working memory and depression papers found evidence of associations but were constrained by statistical power as the studies were designed to have sufficient power for the main analyses. In order to avoid major questions of Type II error, future analysis should be designed with power calculated at either the sex or SGA status level.

In summary, my dissertation provides some limited evidence of associations between early childhood growth in certain periods and both working memory outcomes and lifetime MDD. Some of these outcomes are seen only in certain groups such as positive associations between height growth and some working memory outcomes in males, or in the inverse association between height growth and lifetime MDD in males. Research focused on other growth periods and/or other neurodevelopmental outcomes would fill in the gaps in our knowledge of the association between early childhood height growth and neurodevelopmental outcomes.

Main Figures and Tables

Search Terms
(human, English language, children 0-18 only)
cognition, mental competency, intelligence,
intelligence tests
and
height, child development, adolescent development
not
growth hormone

418 articles

Exclusions for Reason: (n=404)
*reviews, commentary, focus on
specific diseases/disorders, irrelevant
age period, conference abstracts*

14 articles

1 article found in a list of
related citations in PubMed

16 articles
total

Search Terms
(human, English language, children 0-18 only)
cognition, mental competency, intelligence,
intelligence tests
and
height, child development, adolescent development
not
growth hormone

582 articles

Duplicates of PubMed search
(n=301)

Exclusions for Reason: (n=280)
*reviews, commentary, focus on
specific diseases/disorders, wrong age
period, conference abstracts, foreign
language, psychology of size*

1 article

Figure 1. Literature Search Process.
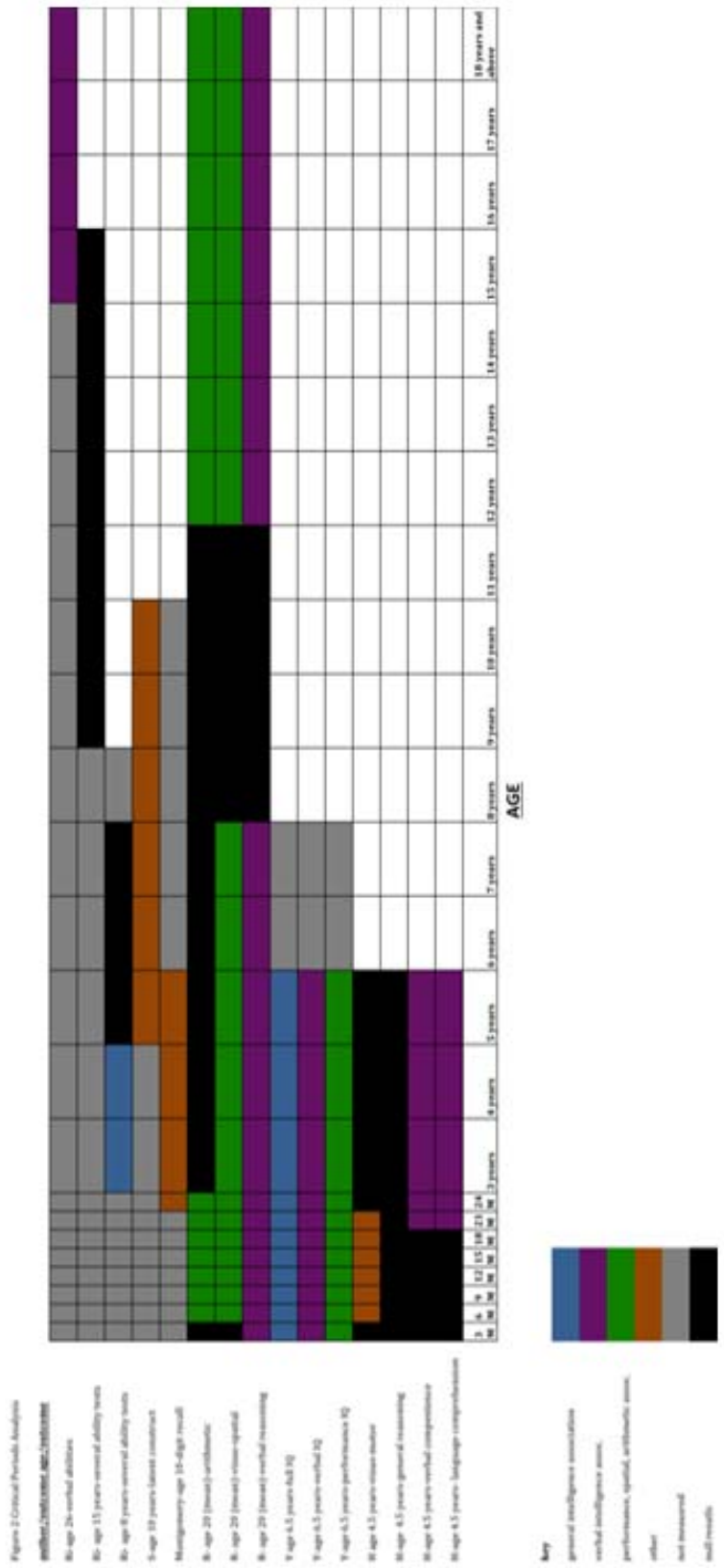
Figure 2. Critical Periods Analysis.
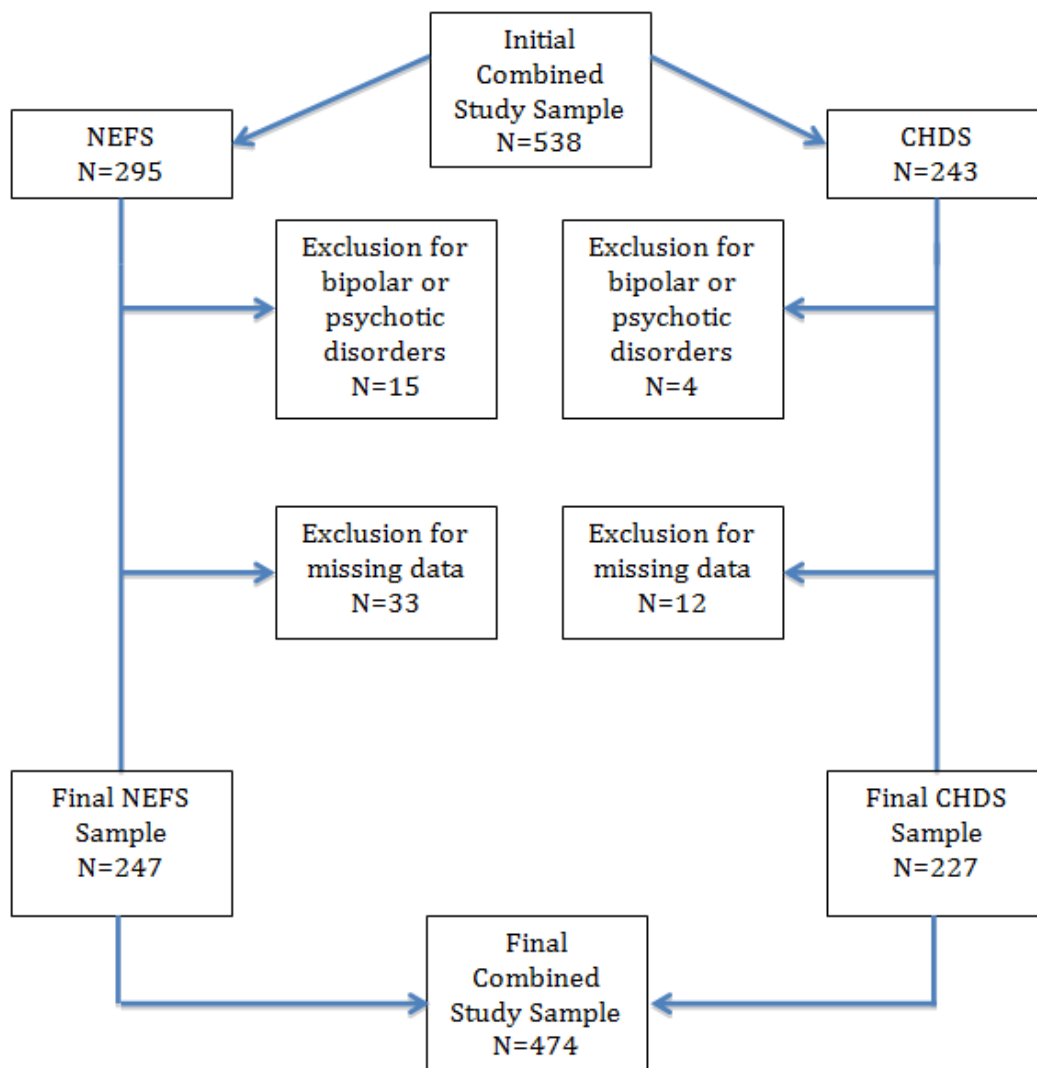
Figure 3. Final study sample after exclusions for certain psychiatric disorders and missing data. NEFS, New England Family Study; CHDA Child Health and Development Studies.

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
Heinonen K, 2008, *Pediatrics*	1056 Finnish children born at term, (37 to 41 weeks) free of major impairments, mental retardation and developmental delay. Births were in 1985-6. Children who were admitted to a NICU were recruited at a Helsinki hospital and other children were recruited from three neighboring hospitals. 57% of the sample had been admitted to the NICU. Loss to follow up was 28% by age 56 months. Those subjects lost to follow up were more likely to have been admitted to the NICU, to have come from less educated families, to have had younger mothers, mothers who smoked during pregnancy and smaller length and size at birth.	Longitudinal. The study is based on data from a prospective birth cohort.	Height growth variables are based on standardized residuals following from the linear regression models.. Height was regressed on previous height measures at earlier points, creating residuals reflecting growth conditional on previous history.	Growth periods are birth to 5 months, 5 to 20 months, and 20 to 56 months. Cognitive abilities were measured at 56 months.	Four measures: 1. Columbia Mental Maturity Scale to measure general reasoning. 2. The Beery scale to measure visual-motor integration. 3. A verbal competence test devised by Kiese and Koseilsi similar to the Peabody picture vocabulary test. 4. Logopädishe Sprachverständ-nis Test to measure language comprehension.	SES, sex, maternal height, breastfeeding at age 5 months, maternal age, multiple pregnancy status, NICU admission. SES was measured as the average of parental education levels.	According to test results in 'Cognitive Ability Measures' column. Results are expressed as increases in cognitive ability test measure score *per a 1 SD increase in height growth* 1. No relationships found. 2. The growth period from ages five to twenty months is associated with the Beery Scale (1.29, 95% CI 0.35, 2.22). 3. The growth period from ages 20 to 56 months is associated with test results (1.57, 95% CI 0.65, 2.49). 4. The growth period from ages 20 to 56 months is associated with test results. (1.03, 95% CI 0.05, 2.01).

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
Yang S, 2011, *International Journal of Epidemiology*	11,899 children enrolled in the Promotion of Breastfeeding Intervention Trial and born in 1996-7 in Belarus. Participants had a gestation of at least 37 weeks and birth weight of at least 2500 grams. Study inclusion was also based on mother's intention to breastfeed, the ability to breastfeed and consent to the breastfeeding trial. There was 18% loss to follow up by age 6.5 years. Those lost to follow up or missing information were more likely to have highly educated fathers with non-manual occupations and to be first born children, but less likely to have mothers with non-manual occupation.	Longitudinal. The study is based on information from a randomized clinical trial.	Standardized height measures were used to derive height growth trajectories over four time periods: prenatal, birth to age 3 months, ages 3 to 12 months and ages 1 to 5 years.	Height at ages 1,2,3,6,9, and 12 months and at varying checkup dates to age 5 years. Cognitive abilities at age 6.5 years.	Wechsler Abbreviated Scales of Intelligence (Russian version).	Maternal and family variables at birth, breastfeeding, parental height and BMI. SES measured as parental occupation and education.	Higher height growth rates in each period were associated with higher full IQ, performance IQ and verbal IQ scores after adjustment for confounders and growth in earlier periods. For each 1 SD of height growth, mean full IQ increased 0.65 points in children ages birth to 3 months, 0.84 points for children ages 3 to 12 months and 0.64 points for children ages 1 to 5 years. The results were similar for Verbal IQ and Performance IQ sub-scales with the relationships somewhat stronger for Verbal IQ. There were no significant differences by sex.

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
Montgomery SM, 2006, *Arch Dis Child*	17,196 mother child pairs enrolled in the 1970 British Birth Cohort Study. This study uses a subgroup of 2296 children. The subgroup is randomly chosen in part and also oversamples small for gestational age, over-mature and multiple birth children. Loss to follow up in the subsample was 28% by year 10. Another 8% were excluded due to missing information. Differences between those lost to follow up and the remaining cohort is not discussed.	Longitudinal and cross sectional. The study is based on data from a prospective birth cohort.	Height growth was measured as the change in height z scores from the beginning to end of the height growth period.	Height measures at ages 22 and 60 months. Cognitive ability test at age 10 years.	Digit recall test.	Sex, multiple births, gestational age. SES was measured as social class (manual, non-manual and other)	*The difference in height z scores from 22 to 60 months was positively related to digit recall scores after including height at age 22 months as a covariate. Mean increase in the digit recall score of 0.35 (p=0.007).*
Silva A, 2006, *Annals of Epidemiology*	17,196 mother-child pairs were enrolled in the 1970 British Birth Cohort Study. This sample excludes non-singleton births reducing sample size 3% to 16,588. Of this reduced sample, the final study sample was 11244, a reduction of	Longitudinal. The study is based on data from a prospective birth cohort. In the	Height in cms.	Height was measured at ages 5 and 10 years. Cognitive ability was measured at age 10 years.	Cognitive function is the latent construct used as an outcome measures. It includes four intelligence and achievement tests: British Ability Scale	Confounders were maternal age, smoking during pregnancy, parity, breast-feeding, gender, reading to child, age	*Using structural equation modeling, the standardized total effect of height at ages 5 and 10 years on the latent cognitive variable was of 0.030 and 0.061, respectively.*

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
	32% due to loss to follow up and missing data. Cases lost to follow up or missing data were more likely to have fathers with manual or managerial professions or to have parents with at the extremes of educational attainment and to have shorter gestational ages and lower birth weights.	structural equation analysis, the variables were birth weight, parental height, gestational age, maternal variables, and ethnicity. SES was represented by a latent variable representing father's social class (based on education) and parent's education.			(two verbal and two non-verbal subscales), and Reading, Maths, and Language Tests (achievement tests).	when the child started school, marital status and ethnicity.	
Richards, 2002, *International Journal of Epidemiology*	This study is based in the 1946 British birth cohort. The initial cohort consisted of 13,867 children or, 93% of those eligible.	Longitudinal. The study is based on informatio	Height was categorized into 5 categories for analysis.	Height at ages 2, 4 and 7 years and cognitive abilities at	Reading comprehension, word pronunciation, vocabulary, non- verbal	Birth weight, current weight, sex, birth order, and maternal age. SES was	A suggestive relationship existed between height at age 7 and cognitive abilities at age 8 (p for trend=0.06). The

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
(analysis with outcome at age 8 years)	The cohort size was reduced to 5,362 including all children of non-manual and agricultural workers and a random sample of other children enrolled in the 1946 British Birth Cohort . All children who were singletons and were not born to unwed mothers were included. At age 8 years, 2,758 children enrolled in the British 1946 birth cohort and had the correct measurements and covariates for this analysis. 51% of the cohort was missing data for this analysis or was lost to follow up by age 8 years. Those lost to follow up were more likely to be of lower education or from a higher social class.	n from a prospective birth cohort		age 8 years.	reasoning.	measured from paternal occupation (6 categories) and mother's education (2 categories).	shortest versus tallest groups had a mean score difference of 0.24 SDs (95% CI=0.06, 0.42). This was reduced by adjustment for height at ages 2 and 4 years (p=0.21). There was a significant association between height at age 4 and cognitive abilities at age 8 (p=0.03). These results imply that height growth between ages 2 and 4 years is associated with cognitive ability at age 8.
(Richards) (analysis with	2,900 children enrolled in the British 1946 birth cohort.	Same as above.	Same as above.	Height at ages 8 and 15 years and	Verbal and nonverbal intelligence (AH4), reading	Same as above.	At age 15 years. a relationship existed between height levels and cognitive

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
outcome at age 15 years)	46% of the cohort was missing data for this analysis or was lost to follow up by age 15 years. Those lost to follow up were more likely to be of lower education or from a higher social class.			cognitive abilities at age 15 years.	comprehension (Watts-Vernon), mathematics.		abilities (p for trend=0.02). The z scores ranged from -0.17 to 0.08 for the lowest to highest height level with the largest change (0.16) between the lowest and second lowest levels. This relationship was reduced by adjustment for height at age 8 years (p for trend =0.32). The effect size changes were not disclosed. This implies that height growth between ages 8 and 15 years is not associated with the measured cognitive abilities at age 15.
(analysis with outcome at ages 26 years)	Children enrolled in the British 1946 birth cohort. At age 26 years, N=2098. 61% of the original cohort was missing data or was lost to follow up by ages 26 and 43 years,	Same as above.	Same as above.	Height at ages 15 and 36 years and cognitive abilities at age 26 years.	At age 26: Reading Comprehension (Watts-Vernon).	Same as above.	Age 26: A significant relationship existed between height level and cognitive abilities (p for trend<0.001). The mean difference in score between the lowest and highest height categories

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
	respectively. Those lost to follow up were more likely to be of lower education or from a higher social class.						was 0.46 SDs (0.95%CI 0.27-0.64). The relationship between height and cognitive abilities was still significant after adjustment for height at age 15 (p=0.001).
Raikonnen K, 2009, *American Journal of Epidemi-ology*	2,786 males born 1934-1944, enrolled in the Helsinki Birth Cohort Study and conscripted by the Finnish Defense Forces between 1952 and 1972. The original birth cohort included 4,630 males that had existing birth and welfare records. The characteristics of conscripts did not differ from the overall birth cohort.	Longitudinal. The study is based on information from a prospective birth cohort.	Height scores (standardized) were used to calculate standardized residuals for each of 5 growth periods.	Height/length measures were obtained at birth, ages 6 months and 2, 7, 11 and at a mean age of 20 years. Cognitive abilities tests were administered at a mean age of 20 years.	The Finnish Defense Forces Basic Ability Tests measures general ability and logical thinking verbal, arithmetic and visuo-spatial tests, the latter being analogous to the Raven's Progressive Matrices. The test scores were standardized.	Maternal height, age and parity, history of breastfeeding, subject age at cognitive testing. SES was measured as father's occupational status.	Height growth was positively related to cognitive abilities in all growth periods except between 7 and 11 years. One SD increase was associated with increases in specific cognitive abilities scores (all statistically significant). *Verbal reasoning* • birth to 0.5 years = 0.05, • 0.5 to 2 years = 0.10, • 2 to 7 years = 0.07, • 11 to 20 years= 0.07. *Visuospatial reasoning* • 0.5 to 2 years = 0.06,

[Table 1] Study	Population/ Exclusions/ Los to Follow Up/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Results
							• 2 to 7 years =0.07, • 11 to 20 years =0.07. *Arithmetic reasoning* • 0.5 to 2 years = 0.05, • 11 to 20 years = 0.05.

Table 1. Characteristics of Studies of the Relationship between Height Growth and Cognitive Abilities.

[Table 2] Study	Population/ Exclusions/ Missing Data	Study Design	Exposure Measure	Exposure/ Outcome Timing	Cognitive Ability Measures	Confounder Control	Analysis Results
Longitudinal studies							
Fisch RO, 1976, *American Journal of Disabled Children*	2,023 children born in Minneapolis, Minnesota between 1959 and 1966 and enrolled in the Collaborative Perinatal Study. Loss to follow up was not discussed in this paper though there were sample sizes at ages 1 and 4 years were lower than at age 7 years.	Longitudinal and cross sectional The study is based on information from a prospective birth cohort. At age 7 years, children were classified by cognitive ability level and then height in each group at 3 ages were compared.	Height in cms.	Height was measured at ages 1, 4 and 7 years. Cognitive abilities were assessed at age 7 years.	Wechsler intelligence scale for children, short form. Children were classified as Superior (IQ>120), Average (IQ from 80 to 119), and Low (IQ below 80).	none	Height of the Low and High intelligence groups were compared with height of Average group at given ages. Height at age 1 year was significantly higher in Average children (75.5 cms) than in Low children (74. cms). Height at age 4 years was significantly higher in Superior children (103.1 cms) versus Average children (101.7cms). Height differences at age 7 years did not significantly differ between groups.

| Humphreys LG, 1985, *Child Development* | 732 girls and 527 boys were recruited from Boston area schools and enrolled in the Harvard Growth Study. | Longitudinal The study is based on information from a prospective birth cohort | Height (the article does not specify the type of measurement) | Attained height and cognitive abilities each year between ages 8-17 | In the 1st to 6th year of the study, the Dearborn Group Test General Examination A and Otis Primary Intelligence Test, Form A. Other tests were used in later years such as the Kuhlman-Anderson Intelligence Test, Terman Group Test of Mental Ability Dearborn Group Test of Intelligence, Detroit Advanced Intelligence Test and the Revised Alpha Examination (Form V). | Ethnicity; SES was measured by parental occupations. | Correlations between height and intelligence were calculated separately by sex. In both sexes positive correlations are higher for attained height at early ages (8-10) and intelligence at age 12. Most correlations in girls are significant at p=0.05. The correlations in boys are less significant and somewhat lower. Partial correlations revealed that controlling for SES and for ethnicity attenuated but did not eliminate the height-intelligence correlations. |

Cross-sectional studies							
Taki Y, 2012, *Neuroimage*	160 children from Japan with normal brain MRIs and were recruited by advertisements at schools. Children were excluded if they had any malignant tumors, head trauma, loss of consciousness of 5 minutes or more, epilepsy, psychiatric disorders or claustrophobia.	Cross sectional The sample was sourced from the general population.	Height	Height and intelligence were measured between ages 5.6 to 18 years.	Wechsler Adult Intelligence Scale for subjects at least 16 years of age. Wechsler Intelligence Scale for Children for subjects younger than 16 years. These tests have a mean of 100 and standard deviation of 15.	Age and sex. SES was measured by family income categorized into 7 levels.	Using partial correlation analysis, height was associated with full scale IQ (C=0.257, p=0.001), verbal IQ (C=0.261, p<0.001) and performance IQ (C=0.187, p=0.019).
Wilson DM, 1986, *Pediatrics* (ages 6-11)	7,119 children in the National Health Examination Survey Cycle II (1963-1965)	Cross-sectional	Height (standardized).	Height and intelligence were measured at ages 6 -11 years in Cycle II	Vocabulary and block design subsets of the Wechsler Intelligence Scale for Children.	Race, family size. SES was measured by family income categorized into 10 levels.	NHANES Cycle II: for males, for every SD in height increase there was a 0.128 point (p<.0001) increase in intelligence score. For females, the increase in intelligence score was 0.070 (p<0.0001) points.

| Lawlor DA, 2005, *J Epidemiol Community Health* | 12,150 children born in Aberdeen, Scotland 1950-1956 and enrolled in the Aberdeen Child Development Survey, a population-based cohort.

4% of the original cohort was either lost to follow up or had missing data by the time of the cognitive testing at age 7. The N at age 7 was 11,679 | Cross-Sectional | Height (standardized) | Ages 7, 9 and 11 years | Age 7-Moray House picture intelligence tests 1 and 2; Age 9-Shonell and Adams essential intelligence tests A and B; Age 11-Moray Test (verbal reasoning 1 and 2). | Pregnancy and maternal characteristics (pregnancy-induced hypertension, antepartum hemorrhage, artificial rupture of membranes, method of delivery, gravidity, illegitimacy, maternal age, maternal height, maternal physical condition); birth weight for gestational age; number of siblings; SES as measured by paternal occupation at time of subject's birth(grades I to V) | Age 7-Mean difference in IQ score was 1.36 points (95% CI 0.92, 1.80) per 1 sd increase in height in females and 0.47 points (95% CI 0.07, 0.86) per 1 sd of height in males.

The results of the analyses at ages 9 and 11 years were noted to have similar results that were not described in the study. |

Richards, 2002, *International Journal of Epidemiology* (analysis at age 8)	5,362 children enrolled in the British 1946 birth cohort. This birth cohort enrolled all children except unmarried mothers. The children of manual workers were over-sampled in this cohort.	Cross-sectional analyses The study is based on information from a prospective birth cohort	Height classified into 5 levels for analysis	Height at age 7 and cognitive abilities at ages 8.	Verbal and nonverbal intelligence (AH4), reading comprehension (Watts-Vernon), mathematics.	Birth weight, current weight, sex, birth order, and maternal age. SES was measured from paternal occupation and mother's education.	A relationship existed between height and levels of cognitive abilities (p for trend=0.02). The z scores ranged from -0.17 to 0.08 for the lowest to highest height level with the largest change (0.16) between the lowest and second lowest levels.
Weinberg WA, 1974, *J Pediatr*	334 white males enrolled in schools in the St. Louis, Missouri area.	Cross sectional Based on information from a cross section of St. Louis schools.	Height	Ages 8.0 to 9.5 yearsí	The Vocabulary, Similarities and Block Design subtests of the Wechsler Intelligence Scale for Children and the Peabody Picture Vocabulary Test was also administered.	SES was measured by the Hollingshead-Redlich Two Factor Index of Social Class Position that weights father's education by four and occupation by 7. This score is then classified into 5 categories of SES.	Partial correlations between height and the WISC score were 0.135 (p<.05) and between height and the PPVT were 0.205 (p<0.001).

Wilson DM, 1986, *Pediatrics* (ages 12-17)	6,768 children in the National Health Examination Survey Cycle III (1966-1970).	Cross sectional	Height (standardized).	Height was measured at ages 12-17 years.	Vocabulary and block design subsets of the Wechsler Intelligence Scale for Children.	Race, family size. SES was measured by family income categorized into 10 levels.	For males, for every SD in height increase a 0.138 point (p<.0001) increase in intelligence score. For females, the increase in intelligence score was 0.145 (p<0.0001) points.
Lawlor DA, 2006, *Paediatric and Perinatal Epidemiology*	3,794 singletons born in Brisbane, Australia between 1981 and 1984 and enrolled in the Mater University study of pregnancy and its outcomes.	Cross-sectional The analysis is based on data from a prospective birth cohort	Height (standardized)	Height and Cognitive Ability at age 14 years.	Raven's standard progressive matrices (Raven's SPM), standardized to a mean of 100 and SD of 15	Sex, maternal age, maternal ethnicity, gravidity, maternal smoking, prenatal stress at delivery, duration of labor, Apgar scores, birth weight for gestational age, breast feeding, BMI. SES was measured by parental education attainment and family income.	For an increase of one sd in height, Raven's score increased by a mean of 0.84 points (95% CI 0.25, 1.43).

Richards, 2002, *International Journal of Epidemiology* Analysis at age 15	5,362 children enrolled in the British 1946 birth cohort. This birth cohort enrolled all children except those with unmarried mothers. The children of manual workers were over-sampled in this cohort. 46% of the cohort was missing data for this analysis or was lost to follow up by age 15 years.	Cross sectional analyses The study is based on information from a prospective birth cohort	Height classified into 5 levels for analysis	Height and cognitive abilities at ages 15 years.	Verbal and nonverbal intelligence (AH4), reading comprehension (Watts-Vernon), mathematics.	Birth weight, current weight, sex, birth order, and maternal age. SES was measured from paternal occupation and mother's education.	A relationship existed between height and levels of cognitive abilities (p for trend=0.02). The z scores ranged from -0.17 to 0.08 for the lowest to highest height level with the largest change (0.16) between the lowest and second lowest levels.

Eide MG, 2007, *Pediatric Research*	317,761 singleton males from the Norwegian Conscript Service; males were conscripted at age 18 between 1984 and 1999. Conscripts exclude: those untraceable (6.2%), permanently disabled men (1.4%) and emigrees (1.0%). 8.5% were excluded because of missing data. Differences between the included and excluded were not discussed.	Cross-sectional This analysis is based on conscript records linked to information from Norwegian national records, the Norwegian Medical Birth Registry and the National Health Insurance Office.	Height (standardized)	Age 18 years	Verbal analogues, number series, geometric figures (Raven's Progressive Matrices).	SES measured by maternal education categorized into 3 levels.	Figure 2 in the article shows mean intelligence scores increasing as height increases, a relationship found at all three maternal education levels. No statistics on this relationship were presented.

Tuvemo T, 1999, *Hormone Research*	32,887 Swedish men age 18 years conscripted into military service in 1994. This group excluded 15 % of the original cohort (N=38,900). Those excluded had missing data or severe handicaps, congenital malformations or chronic disease.	Cross sectional This analysis is based on an original cohort of all men born in Sweden in 1976 and later conscripted into military service.	Height (standar-dized) was classified into categories: very short men: (-3 SDs of height or shorter; and short men (-2 SDs of height but not -3 or more). Other men were classified as 'normal'.	Approximately age 18	The test measured four areas with equal weight: logical/inductive, verbal, spatial and theoretical/technical.	none	A continuous measure of height correlated with intelligence (r=0.14, p<0.001). Mean intelligence score rose across SD levels with the highest level in those 2-3 SDs over the mean attained height, declining again in taller categories.
Teasdale TW, 1989, *British Medical Journal*	Danish men born during 1939-1967 and in 1985. About 8% are exempted based on medical reasons. These men were grouped into 5 categories by birth year: 1939-1943: n=7,332; 1944-1948 n=9182; 1943-1953 n=7,466; 1954-1958 n= 6,773; 1964-67 n=13,226.	Cross sectional; also looked at trends in cross sectional relationships over time with the different cohorts over time.	Height (cms)	Age 18 years	The draft board's intelligence test-details not provided.	none	The correlation of intelligence scores with attained height were highly significant for all cohorts (p<.001) and declined from 0.269 points for the 1939-1943 cohort to 0.195 points for the 1964-1967 cohort.

Richards, 2002, *International Journal of Epidemiology*	2,098 children enrolled in the British 1946 birth cohort. This birth cohort enrolled all children except those who were 'illegitimate'. The children of manual workers were over-weighted in this cohort.	Cross sectional analyses The study is based on information from a prospective birth cohort	Height classified into 5 levels for analysis	Height and cognitive abilities at age 26 years.	reading comprehension (Watts-Vernon, with additional questions of increased difficulty), mathematics.	Birth weight, current weight, sex, birth order, and maternal age. SES was measured from paternal occupation and mother's education.	A relationship existed between height and levels of cognitive abilities (p for trend<0.001). The z scores ranged from -0.17 to 0.16 for the lowest to highest height level.
Richards, 2002, *International Journal of Epidemiology*	2,136 children enrolled in the British 1946 birth cohort. This birth cohort enrolled all children except those who were 'illegitimate'. The children of manual workers were over-weighted in this cohort.	Cross sectional analyses The study is based on information from a prospective birth cohort	Height classified into 5 levels for analysis	Height and cognitive abilities at age 43 years.	Verbal memory measured by a test devised by the MRC National Survey of Health and Development, the organization of the 1946 British Birth Cohort.	Birth weight, current weight, sex, birth order, maternal age. SES was measured from paternal occupation and mother's education.	A relationship existed between height and levels of cognitive abilities (p for trend=0.01). The z scores ranged from -0.17 to 0.16 for the lowest to highest height level with the largest change (0.17) between the lowest and second lowest levels.

Table 2. Characteristics of Studies of the Relationship between Height and Cognitive Abilities. Studies are organized by type of study design.

Characteristics	CHDS			NEFS			
	N Total	Mean or Percentage	Standard Deviation	N Total	Mean or Percentage	Standard Deviation	P value*
Total	174	100%	-	194	100%	-	NA
Sex (% male)	174	48%	-	194	44%	-	0.30
Subject Age at Interview (years)	174	43.4	(2.1)	193	44.1	(2.4)	<0.01
Race	174	-	-	194	-	-	<0.01
White	115	66%	-	179	92%	-	-
Other	59	34%	-	15	8%	-	-
Maternal Age (years)	174	26.9	(5.6)	194	24.7	(5.2)	<0.01
Maternal Education	174	-	-	193	-	-	0.01
High School or less	87	50%	-	75	39%	-	-
Some college	60	34%	-	94	49%	-	-
College or higher	27	16%	-	24	12%	-	-
Maternal Height (inches)	167	64.1	(2.5)	148	63.5	(2.6)	0.04
Maternal Parity (number)	174	1.4	(1.1)	194	1.5	(1.1)	0.38
Maternal Smoking at Birth	166	39%	-	194	52%	-	0.03

*The p values are based on a t test of the differences between the 2 groups where there is a standard deviation measure. The p values are based on a chi square test of the differences where there are proportions.
NA, not applicable.

Table 3. Chapter 2-Subject Characteristics.

Characteristics	CHDS			NEFS			P value**
	N Total	Mean or Percentage	standard deviation	N Total	Mean or Percentage	standard deviation	
Birth weight (lbs)	174	7.5	(7.5)	193	7.1	(0.8)	<0.01
Birth length (ins)	174	20.4	(1.0)	194	20.0	(0.8)	<0.01
Gest. age (wks)	174	40.0	(1.2)	193	40.3	(1.2)	0.02
Height at age 4 months (ins.)*	166	24.5	(0.9)	194	24.8	(1.0)	<0.01
Height at age 1 year (ins.)*	158	29.3	(1.2)	194	29.2	(1.2)	0.44
Height at age 4 years (ins.)*	148	40.3	(2.0)	194	39.2	(1.7)	<0.01
Height Percentile at birth	174	48.8%	(28.3)	194	47.7%	(26.2)	0.70
Height Percentile at age 4 months	166	46.0%	(27.9)	190	49.8%	(28.9)	0.21
Height Percentile at age1 year	158	44.6%	(27.4)	193	47.0%	(29.9)	0.44
Height Percentile at age 4 years	148	47.8%	(29.0)	194	45.9%	(29.1)	0.55
Height Percentile change from birth to age 4 months	166	-3.1%	(27.5)	190	1.9%	(30.1)	0.05
Height percentile change from ages 4 months to 1 year	150	-0.1%	(18.2)	189	-3.1%	(24.9)	0.22
Height percentile change from ages 1 to 4 years	139	3.9%	(21.4)	193	-0.9%	(22.5)	0.05
Verbal Recall-California Verbal Learning Test	168	27.6	(6.2)	194	26.0	(5.7)	0.01
Attention with Interference- (Seidman CPT)	173	9.9	(3.4)	193	9.2	(2.9)	0.03
Attention- (Seidman CPT)	173	-	-	193	-	-	0.42
AV score = 18	137	79%	-	146	76%	-	-
AV score < 18	36	21%	-	47	24%	-	-
Processing Speed- WAIS Digit Symbol Test, scaled score	171	11.2	(3.2)	193	10.3	(2.7)	<0.01

*These values are imputed to the exact age as described in the methods section.
** The p values are based on a t test of the differences between the 2 groups where there is a standard deviation measure. The p values are based on a chi square test of the differences where there are proportions.

Table 4. Height and Height Growth Measures, Working Memory Test Scores

	Height Percentile Change								
	Unadjusted Model			Base Model			Fully-Adjusted Model		
Working Memory Outcome Variable	Birth to 4 months	4 months to 1 year	1 to 4 years	Birth to 4 months	4 months to 1 year	1 to 4 years	Birth to 4 months	4 months to 1 year	1 to 4 years
	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N
Child Health and Development Studies									
Verbal Recall	0.07 (0.18) 0.70 160	0.05 (0.27) 0.85 144	0.49 (0.24) 0.05 133	0.12 (0.20) 0.55 160	0.07 (0.30) 0.82 144	0.46 (0.25) 0.08 133	0.21 (0.22) 0.34 154	0.18 (0.31) 0.57 138	0.47 (0.28) 0.11 126
Attention with Interference	-0.11 (0.10) 0.28 165	0.43 (0.15) <0.01 149	0.02 (0.13) 0.88 138	-0.07 (0.11) 0.56 165	0.46 (0.16) <0.01 149	0.03 (0.14) 0.82 138	-0.04 (0.12) 0.75 159	0.61 (0.18) <0.01 143	0.08 (0.16) 0.63 131
Attention	-0.10 (0.06) 0.12 165	0.05 (0.12) 0.69 149	-0.05 (0.10) 0.58 138	-0.17 (0.08) 0.03 165	-0.04 (0.12) (0.73) 149	0.11 (0.10) 0.28 138	-0.16 (0.09) 0.07 159	0.09 (0.14) 0.53 143	-0.04 (0.12) 0.76 131
Processing Speed	0.05 (0.09) 0.56 163	-0.01 (0.14) 0.94 147	0.07 (0.11) 0.55 136	0.06 (0.10) 0.58 163	-0.02 (0.15) 0.89 147	0.07 (0.12) 0.56 136	0.10 (0.11) 0.34 157	0.11 (0.16) 0.48 141	0.20 (0.12) 0.12 129
New England Family Study									
Verbal Recall	-0.03 (0.14) 0.79 190	0.21 (0.17) 0.22 189	-0.34 (0.18) 0.07 193	-0.20 (0.15) 0.19 190	0.24 (0.18) 0.17 189	-0.31 (0.20) 0.12 193	-0.29 (0.16) 0.07 190	0.26 (0.19) 0.17 189	-0.30 (0.20) 0.13 193
Attention with Interference	-0.02 (0.07) 0.82 189	0.02 (0.09) 0.80 188	0.01 (0.10) 0.90 192	-0.04 (0.08) 0.63 189	-0.02 (0.10) 0.82 188	-0.04 (0.11) 0.72 192	-0.10 (0.09) 0.25 189	-0.04 (0.10) 0.67 188	-0.07 (0.11) 0.54 192
Attention	0.02 (0.06) 0.69 189	0.00 (0.06 0.97 189	-0.09 (0.08) 0.26 192	0.04 (0.06) 0.54 189	-0.02 (0.07) 0.76 188	-0.06 (0.08) 0.48 192	0.04 (0.07) 0.58 189	-0.02 (0.08) 0.83 188	-0.07 (0.10) 0.45 192
Processing Speed	-0.08 (0.06) 0.22 182?	0.12 (0.07) 0.13 188	-0.09 (0.08) 0.26 192	-0.05 (0.07) 0.48 189	0.19 (0.08) 0.02 188	0.01 (0.09) 0.91 192	-0.11 (0.07) 0.14 189	0.14 (0.08) 0.10 188	0.01 (0.09) 0.95 192

b, estimated beta; sd, standard deviation.

Table 5a. Associations Between a 10% Height Percentile Increase and Working Memory Outcomes. (Base model adjusted for sex and height percentile at the beginning of the percentile height growth periods. The fully adjusted model also controls for offspring age at interview, offspring race, height percentile at the beginning of the height percentile change interval, maternal age, maternal education, maternal height, maternal smoking, parity and sex).

	Height Percentile Change		
Working Memory Outcome Variable	**Birth to 4 months** *OR* *95% CI* *N*	**4 months to 1 year** *OR* *95% CI* *N*	**1 to 4 years** *OR* *95% CI* *N*
Child Health and Development Studies			
Attention	0.85 (0.71, 1.02) 159	1.09 (0.83, 1.44) 143	0.96 (0.76, 1.22) 131
New England Family Study			
Attention	1.04 (0.91, 1.19) 189	0.98 (0.84, 1.15) 188	0.93 (0.76, 1.13) 192

OR, odds ratio; *CI*, confidence interval.

Table 5b. Odds Ratios for an Attention Score Increase Given a 10% Height Percentile Increase. The fully adjusted model controls for offspring age at interview, offspring race, height percentile and the beginning of the height percentile change interval, maternal age, maternal education, maternal height, maternal smoking, parity and sex.

Working Memory Outcome	Height Percentile Change								
	Fully adjusted model-Females			Fully adjusted model -Males					
	Birth to 4 mos.	4 mos. to 1 year	1 to 4 years	Birth to 4 mos.	4 mos. to 1 year	1 to 4 years	Birth to 4 mos.	4 mos to 1 year	1 to 4 years
	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	b (sd) P Value N	P Value*	P Value*	P Value*
Child Health and Development Studies									
Verbal Recall	0.14 (0.28) 0.63 80	-0.10 (0.40) 0.81 70	0.64 (0.38) 0.13 64	0.10 (0.35) 0.77 74	0.67 (0.54) 0.26 68	0.42 (0.28) 0.15 62	0.93	0.25	0.72
Attention With Interference	-0.09 (0.15) 0.53 83	0.42 (0.22) 0.08 73	-0.04 (0.22) 0.84 67	-0.004 (0.21) 0.98 76	0.90 (0.29) 0.02 70	0.04 (0.16) 0.80 64	0.74	0.19	0.76
Attention	-0.17 (0.10) 0.10 83	0.05 (0.14) 0.73 73	-0.01 (0.18) 0.97 67	-0.12 (0.05) 0.13 76	0.20 (0.21) 0.34 70	-0.06 (0.12) 0.63 64	0.65	0.55	0.82
Processing Speed	0.23 (0.15) 0.14 82	-0.11 (0.11) 0.45 72	0.47 (0.15) 0.01 66	-0.01 (0.16) 0.95 75	0.43 (0.23) .11 69	0.18 (0.13) 0.17 63	0.28	0.03	0.14
New England Family Study									
Verbal Recall	-0.54 (0.24) 0.02 106	-0.10 (0.28) 0.74 106	-0.43 (0.29) 0.14 109	-0.09 (0.21) 0.66 84	0.73 (0.23) 0.001 83	-0.01 (0.26) 0.96 84	0.16	0.02	0.28
Attention With Interference	-0.14 (0.12) 0.23 105	-0.22 (0.14) 0.11 105	0.01 (0.14) 0.95 108	-0.10 (0.13) 0.47 84	0.11 (0.17) 0.49 83	-0.17 (0.18) 0.37 84	0.82	0.13	0.43
Attention	0.03 (0.10) 0.79 105	-0.08 (0.10) 0.39 105	-0.18 (0.12) 0.14 108	0.09 (0.12) 0.47 84	0.13 (0.18) 0.48 83	0.17 (0.17) 0.31 84	0.70	0.20	0.09
Processing Speed	-0.18 (0.10) 0.08 105	0.14 (0.11) 0.22 105	-0.04 (0.12) 0.75 108	-0.07 (0.11) 0.49 84	0.10 (0.13) 0.42 83	0.02 (0.15) 0.87 84	0.46	0.81	0.75

p values were calculated for chi-square test on the differences between females and males.
b, estimated beta sd, standard deviation.

Table 6. Associations between Height Percentile Change and Working Memory Outcomes Stratified by Sex. The fully adjusted model adjusts For height percentile at the beginning of the height percentile growth period, for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity.

Characteristics	N Total	CHDS Mean or Percentage (sd)	standard deviation	N Total	NEFS Mean or Percentage (sd)	standard deviation	P Value
Total	184	100%	-	209	100%	-	NA
Sex (% male)	184	50%	-	209	45%	-	0.32
Age at interview (years)	184	43.4	(2.0)	199	44.1	(2.4)	<0.01
Race	184	-	-	200	-	-	<0.01
White	124	67%	-	185	92%	-	
Other	60	33%	-	15	8%	-	
Family History Of Mental Illness	184	44%	-	167	57%	-	0.02
Maternal Age (years)	184	27.0	(5.6)	200	24.6	(5.1)	<0.01
Maternal Education	184	-	-	199	-	-	<0.01
High School or less	94	51%	-	27	38%	-	
Some college	61	33%	-	96	48%	-	
College or higher	29	16%	-	76	14%	-	
Maternal Height (inches)	177	64.2	(2.5)	154	63.5	2.6	0.01
Maternal Parity (number)	184	1.4	(1.1)	200	1.4	(1.1)	>0.99
Maternal Smoking at Birth (number of smokers)	176	38%	-	200	52%	-	<0.01

*The p values are based on a t test of the differences between the 2 groups where there are means and a standard deviation measure. The p values are based on a chi square test of the differences where there are proportions.
NA, not applicable.

Table 7. Chapter 3-Subject Characteristics.

Characteristics	CHDS			NEFS			
	N Total	Mean or Percentage	standard deviation	N Total	Mean or Percentage	% or standard deviation	P Value
Birth weight (lbs)	184	7.5	(0.9)	208	7.2	(0.9)	<0.01
Birth length (ins)	184	20.4	(1.0)	209	20.0	(0.8)	<0.01
Gestational age (weeks)	184	40.0	(1.2)	199	40.3	(1.2)	0.02
Height at age 4 months (ins.)*	176	24.6	(0.9)	204	24.8	(1.0)	0.04
Height at age 1 year (ins.)*	168	29.3	(1.2)	208	29.2	(1.2)	0.42
Height at age 4 years (ins.)*	158	40.3	(2.0)	209	39.2	(1.7)	<0.01
Height % at birth**	184	49.3%	(28.1)	209	48.0*	(26.4)	0.64
Height % at age 4 months**	176	46.4%	(27.8)	204	49.6*	(28.5)	0.27
Height % at age1 year**	168	45.2%	(27.3)	208	46.5%	(29.4)	0.66
Height % at age 4 years**	158	49.3%	(29.4)	204	46.5%	(28.8)	0.36
Height % change from birth to age 4 months	176	-3.2%	(27.5)	204	1.1%	(29.5)	0.14
Height percentile change from ages 4 months to 1 year	160	0.03%	(18.5)	203	-3.2%	(24.9)	0.17
Height percentile change from ages 1 year to 4 years	149	4.6%	(21.2)	208	0.2%	(22.4)	0.06
Lifetime MDD prevalence	184	25%	-	208	38%	-	0.05

*These values are imputed to the exact age as described in the methods section.
** The p values are based on a t test of the differences between the 2 groups where there is a standard deviation measure. The p values are based on a chi square test of the differences where there are proportions.

Table 8. Height and Height Growth Measures, Lifetime MDD Prevalence.

Outcome variable	Height Percentile Change								
	Child Health and Development Studies								
	Unadjusted Model			Base Model			Fully Adjusted Model		
	Birth to 4 Months	4 Months to 1 Year	One to 4 Years	Birth to 4 Months	4 Months to 1 Year	One to 4 Years	Birth to 4 Months	4 Months to 1 Year	One to 4 Years
	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N	OR (95% CI) N
Lifetime MDD	1.07 (0.95, 1.21) 176	1.05 (0.84, 1.31) 160	1.06 (0.91, 1.24) 149	1.02 (0.89, 1.17) 176	1.04 (0.84, 1.29) 160	1.05 (0.88, 1.25) 149	0.98 (0.82, 1.17) 167	1.00 (0.79, 1.26) 151	0.99 (0.81, 1.20) 139
	New England Family Study								
Lifetime MDD	1.01 (0.91, 1.12) 204	0.94 (0.84, 1.06) 203	0.99 (0.88, 1.11) 208	0.96 (0.85, 1.08) 204	0.91 (0.80, 1.04) 203	0.99 (0.86, 1.14) 208	0.97 (0.86, 1.09) 204	0.96 (0.82, 1.12) 203	0.94 (0.80, 1.10) 208

OR, log odds ratio; *CI*, confidence interval.

Table 9. Odds Ratios for Lifetime MDD Given a 10% Increase in Height Percentile. The fully adjusted model controls for sex, height percentile at the beginning of the height percentile change interval, subject race, maternal age, maternal education, parity, offspring family history of mental illness, offspring age at interview.

Outcome variable	Height Percentile Change								
	Fully adjusted model female			Fully adjusted model males			Birth to 4 mos.	4 mos to 1 year	1 to 4 years
	Birth to 4 months	4 months to 1 year	One to 4 years	Birth to 4 months	4 months to 1 year	One to 4 years			
	OR 95% CI N	OR 95% CI N	OR 95% CI N	OR 95% CI N	OR 95% CI N	OR 95% CI N	P Value*	P Value*	P Value*
	Child Health and Development Studies								
Lifetime MDD	0.93 (0.69, 1.25) 84	1.17 (0.84, 1.63) 74	0.99 (0.73, 1.35) 68	1.13 (0.86, 1.48) 83	0.90 (0.69, 1.19) 77	1.04* (0.76, 1.42) 71	0.35	0.20	0.86
	New England Family Study								
Lifetime MDD	1.07 (0.90, 1.28) 112	1.04 (0.85, 1.27) 112	1.01 (0.83, 1.23) 115	0.74 (0.58, 0.97) 92	0.85 (0.67, 1.08) 91	0.81 (0.60, 1.09) 93	0.02	0.37	0.22

*This result was calculated using an independent correlation structure instead of a working correlation structure.
OR, log odds ratio

Table 10. Odds Ratios for Lifetime MDD Given a 10% Increase in Height Percentile Change with Results Stratified by Sex. The fully adjusted model controls for sex, height percentile at the beginning of the height percentile change interval, subject race, maternal age, maternal education, parity, offspring family history of mental illness, offspring age at interview.

			Child Health and Development Studies				
			Growth Period				
Outcome Variable	Exposure Variable	N	Birth to 4 months	N	4 month to 1year	N	1 Year to 4 years
			b (sd) P value		b (sd) P value		b (sd) P value
Lifetime MDD	HPC	167	-0.02 (0.10) 0.84	151	*	133	-0.01 (0.11) 0.89
	SGA		- 1.17 (0.79) 0.14				-0.86 (0.80) 0.29
	HPC*SGA		-0.82 (0.44) 0.06				0.39 (0.23) 0.10

*model did not converge

b, estimated beta; sd, standard deviation

Table 11a. Analysis of Effect Modification by Small for Gestational Age (SGA) Status in the Relationship Between Height Percentile Change and Lifetime MDD in the Child Health and Development Studies Cohort. Model is adjusted for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, percentile height at beginning of growth period, sex.

New England Family Study							
			Growth Period				
Outcome Variable	Exposure Variables	N	Birth to 4 months	N	4 month to 1year	N	1 Year to 4 years
			b (sd) *P Value*		*b (sd)* *P Value*		*b (sd)* *P Value*
Lifetime MDD	HPC	203	-0.06 (0.07) 0.39	203	0.06 (0.08) 0.72	208	-0.05 (0.26) 0.51
	SGA		-0.09 (0.55) 0.86		-0.13 (0.57) 0.82		-0.17 (0.55) 0.75
	HPC *SGA		0.20 (0.15) 0.19		0.14 (0.20) 0.51		-0.11 (0.26) 0.65

b, estimated beta; *sd*, standard deviation

Table 11b. Analysis of Effect Modification by Small for Gestational Age Status in the Relationship between Height Percentile Change and Lifetime MDD in the New England Family Study Cohort. Model is adjusted for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, percentile height at beginning of growth period, sex)
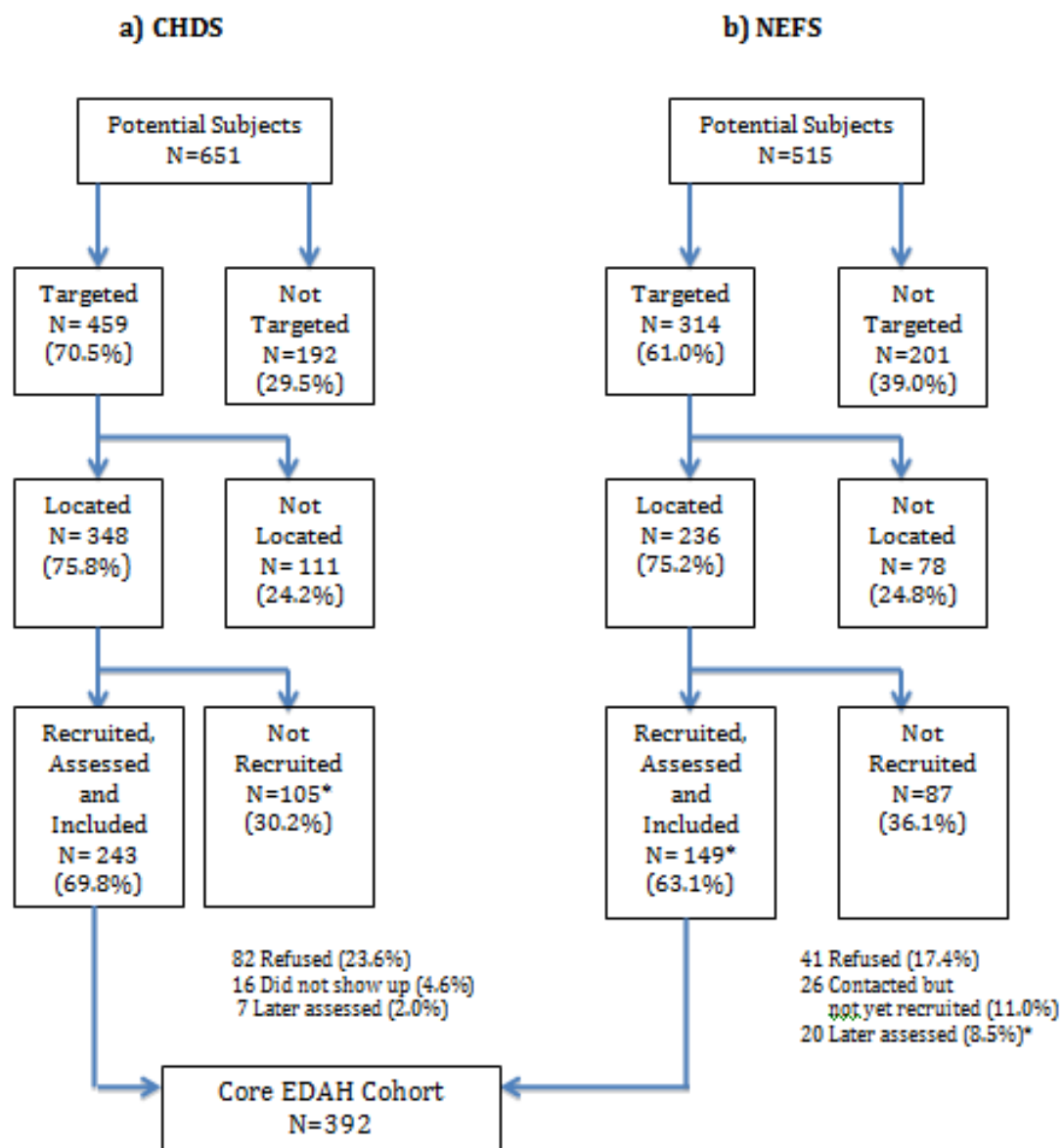
Supplemental Figures and Tables

a) CHDS

```
        Potential Subjects
            N=651

   Targeted              Not
   N= 459             Targeted
   (70.5%)            N=192
                      (29.5%)

   Located               Not
   N= 348             Located
   (75.8%)            N= 111
                      (24.2%)

   Recruited,            Not
   Assessed          Recruited
   and               N=105*
   Included          (30.2%)
   N= 243
   (69.8%)

                   82 Refused (23.6%)
                   16 Did not show up (4.6%)
                   7 Later assessed (2.0%)

           Core EDAH Cohort
                N=392
```

b) NEFS

```
        Potential Subjects
            N=515

   Targeted              Not
   N= 314             Targeted
   (61.0%)            N=201
                      (39.0%)

   Located               Not
   N= 236             Located
   (75.2%)            N= 78
                      (24.8%)

   Recruited,            Not
   Assessed          Recruited
   and               N=87
   Included          (36.1%)
   N= 149*
   (63.1%)

                   41 Refused (17.4%)
                   26 Contacted but
                      not yet recruited (11.0%)
                   20 Later assessed (8.5%)*
```

Supplemental Figure 1. Early Determinants of Adult Health (EDAH) cohort formation. (a) Child Health and Development Study (CHDS) core sample: recruitment flowchart (*7 participants were later assessed but not in the current dataset) and (b) New England Family Study (NEFS) core sample: recruitment flowchart (*20 participants were later assessed but are not in the current dataset).
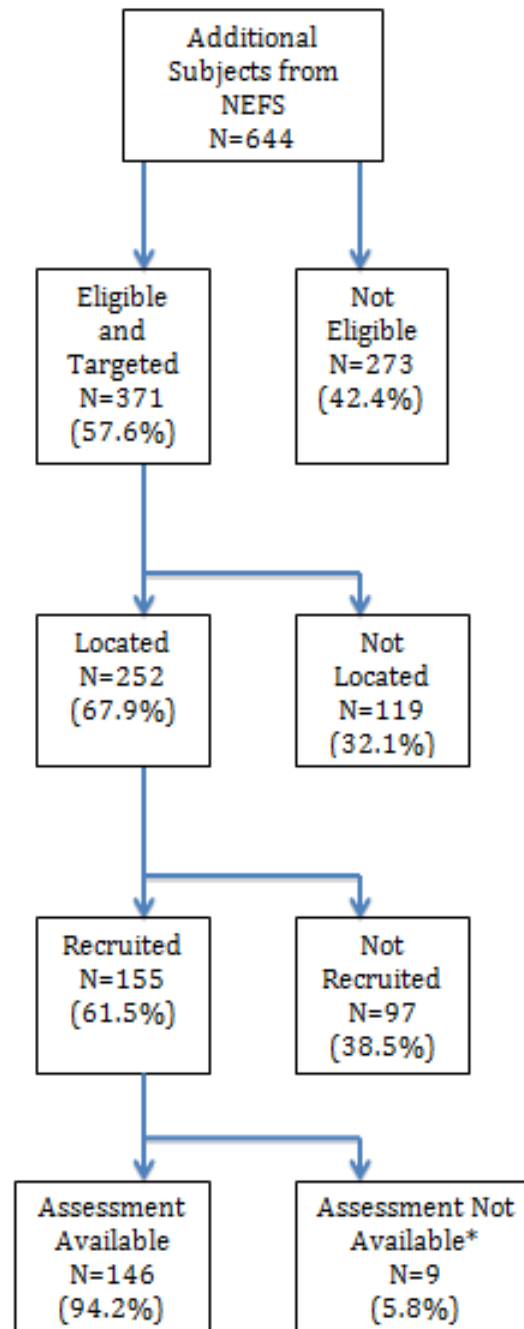
Supplemental Figure 2. Fetal Antecedents of Major Depression and Cardiovascular Disease (MDCVD) cohort formation. *These assessments were not available in time for inclusion in the dataset.
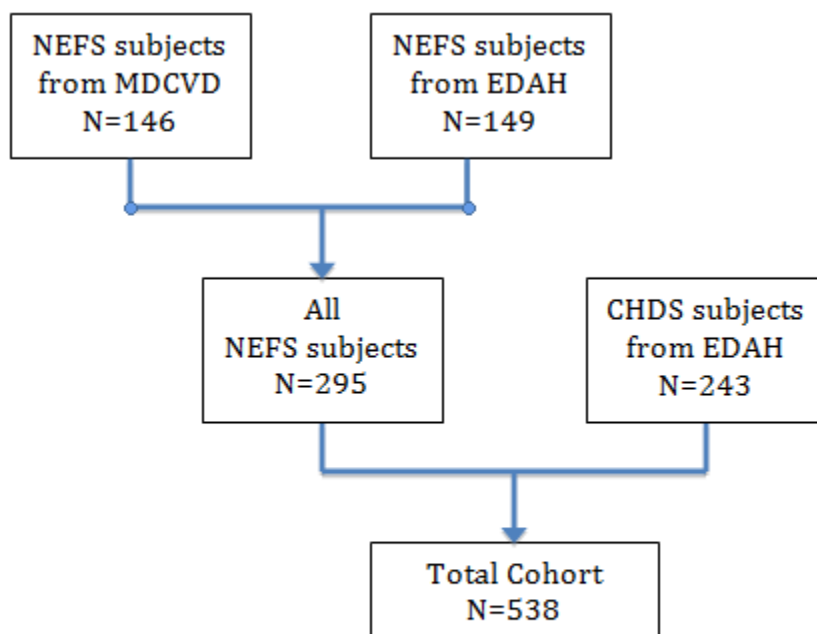
Supplemental Figure 3. Formation of the Study Cohort Before Exclusions

Percentile Height Change Periods	CHDS N	NEFS N
Birth to 4 months	166	190
4 months to 1 year	150	189
1 year to 4 years	139	193

Supplemental Table 1. Chapter 2-Number of Subjects in Study Dataset Groups by Cohort and Growth Period Percentile.

Cohort	Percent of Observations with Missing Covariate Data		
	Height Growth from Birth to Age 4 Months	Height Growth from Ages 4 Months to 1 Year	Height Growth from Ages 1 Year to 4 Years
CHDS cohort	3%-4%	3%-4%	3%-4%
NEFS cohort	25%-29%	25%-28%	25%-27%

Supplemental Table 2. Chapter 2-Missing Covariates

	Height Percentile Change		
Working Memory Outcome	Birth to Age Four Months	Age 4 Months To One Year	Ages 1 to Four Years
	T b (sd) p value N	T b (sd) p value N	T b (sd) p value N
	Child Health and Development Studies		
Verbal Recall	1 -1.80 (1.37) 0.20 2 -2.00 (1.21) 0.11 154	1 -1.5 (1.36) 0.28 2 -0.05 (1.24) 0.97 138	1 -2.94 (1.35) 0.04 2 -2.24 (1.30) 0.10 126
Attention With Interference	1 0.07 (0.80) 0.93 2 -0.18 (0.72) 0.81 159	1 -2.00 (0.78) 0.02 2 -0.74 (0.73) 0.33 143	1 -0.12 (0.82) 0.89 2 -0.26 (0.78) 0.74 131
Attention	1 0.91(0.56) 0.11 2 0.30 (0.48) 0.54 159	1 0.35 (0.58) 0.55 2 0.29 (0.58) 0.62 143	1 -0.32 (0.59) 0.58 2 0.56 (0.60) 0.35 131
Processing Speed	1 -0.75 (066) 0.26 2 0.65 (0.59) 0.28 157	1 -0.19 (0.67) 0.77 2 0.92 (0.62) 0.14 141	1 -0.90 (0.62) 0.16 2 0.18 (0.58) 0.76 129
	New England Family Study		
Verbal Recall	1 0.98 (1.08) 0.36 2 1.72 (0.99) 0.08 189	1 -1.00 (1.11) 0.35 2 0.64(1.08) 0.54 188	1 0.82 (1.08) 0.45 2 0.21 (1.01) 0.83 192
Attention With Interference	1 0.44 (0.57) 0.44 2 0.12 (0.53) 0.82 188	1 0.29 (0.51) 0.61 2 0.21 (0.56) 0.71 187	1 0.41 (0.57) 0.47 2 0.33 (0.53) 0.53 191
Attention	1 -0.05 (0.08) 0.50 2 -0.04 (0.07) 0.54 188	1 -0.05 (0.08) 0.54 2 -0.08 (0.07) 0.21 187	1 0.11 (0.09) 0.22 2 0.08 (0.07) 0.28 191
Processing Speed	1 0.39 (0.48) 0.41 2 0.54 (0.44) 0.22 188	1 -0.90 (0.47) 0.06 2 0.00 (0.46) 0.99 187	1 -0.30 (0.48) 0.53 2 -0.16 (0.45) 0.72 191

T, tertile; 1, lowest tertile, 2, middle tertile

Supplemental Table 3. Associations Between Tertiles of Height Percentile Growth and Working Memory Outcomes. Model is adjusted for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, percentile height at beginning of growth period and sex.

Working Memory Outcome Variable	Predictor Variables	N	Birth to 4 months b (sd) P value	N	4 month to 1year b (sd) P value	N	1 Year to 4 years b (sd) P value
					Height Percentile Change		
					Child Health and Development Studies		
Verbal Recall	HPC	154	0.14 (0.21) 0.53	138	0.17 (0.31) 0.59	126	0.34 (0.28) 0.73
	SGA		-1.88 (1.83) 0.31		-0.35 (1.93) 0.86		-0.76 (2.23) 0.73
	HPC*SGA		1.24 (0.79) 0.13		-0.94 (1.30) 0.48		0.02 (0.16) 0.91
Attention with Interference	HPC	159	-0.07 (0.12) 0.55	143	0.53 (0.17) <0.01	131	0.02 (0.16) 0.91
	SGA		1.09 (1.12) 0.34		1.20 (1.14) 0.30		1.03 (1.37) 0.46
	HPC*SGA		0.38 (0.50) 0.45		-0.59 (0.78) 0.45		0.10 (0.68) 0.88
Attention	HPC	159	-0.15 (0.09) 0.10	143	0.10 (0.14) 0.50	131	0.03 (0.11) 0.75
	SGA		1.11 (0.78) 0.16		0.80 (0.68) 0.24		1.25 (0.83) 0.13
	HPC*SGA		0.32 (0.25) 0.20		-0.03 (0.40) 0.94		-0.09 (0.33) 0.78
Processing Speed	HPC	157	0.07 (0.11) 0.54	141	0.02 (0.15) 0.88	129	0.15 (0.13) 0.26
	SGA		0.25 (0.98) 0.80		0.49 (1.00) 0.63		0.18 (1.22) 0.88
	HPC*SGA		0.27 (0.40) 0.50		0.52 (0.63) 0.42		0.07 (0.52) 0.89

b, beta; sd, standard deviation.

Supplemental Table 4a. Effect Modification by Small for Gestational Age Status (SGA) in the Relationship between Height Percentile Change (HPC) and Working Memory Outcomes in the Child Health and Development Studies Cohort. Model is adjusted for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, percentile height at beginning of growth period, sex and SGA. Effect modification is analyzed by entering an interaction term (SGA*HPC) into the SAS code.

Working Memory Outcome Variable	Predictor Variables	Height Percentile Change					
		New England Family Study					
		N	Birth to 4 months	N	4 month to 1year	N	1 Year to 4 years
			b (sd) P Value		b (sd) P Value		b (sd) P Value
Verbal Recall	HPC	190	-0.24 (0.41) 0.56	189	0.32 (0.43) 0.32	193	0.78 (0.56) 0.16
	SGA		-0.01 (0.22) 0.03		2.94 (1.35) 0.03		2.55 (1.33) 0.06
	HPC *SGA		0.06 (0.43) 0.89		-0.5 (0.46) 0.91		0.51 (0.57) 0.37
Attention With Interference	HPC	189	-0.01 (0.22) 0.96	188	-0.24(0.23) 0.30	192	0.26 (0.30) 0.39
	SGA		0.85 (0.78) 0.28		0.74 (0.74) 0.32		0.87 (0.74) 0.22
	HPC *SGA		-0.10 (0.23) 0.66		0.22 (0.25) 0.37		0.37 (0.31) 0.23
Attention	HPC	189	0.04 (0.07) 0.60	188	0.05 (0.09) 0.62	192	-0.12 (0.19) 0.54
	SGA		-0.29 (0.68) 0.67		0.32 (0.67) 0.64		0.39 (0.67) 0.56
	HPC *SGA		-0.06 (0.09) 0.50		0.07 (0.10) 0.45		0.06 (0.19) 0.76
Processing Speed	HPC	189	-0.18 (0.18) 0.31	188	0.01 (0.19) 0.94	192	0.20 (0.24) 0.31
	SGA		-0.22 (0.65) 0.73		0.11 (0.62) 0.86		-0.14(0.60) 0.81
	HPC* SGA		0.09 (0.19) 0.65		0.15 (0.20) 0.45		0.23 (0.25) 0.34

b, beta; sd, standard deviation.

Supplemental Table 4b. Effect Modification by Small for Gestational Age Status (SGA) in the Relationship between Height Percentile Change (HPC) and Working Memory Outcomes in the New England Family Study Cohort. Model is adjusted for age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, percentile height at beginning of growth period, sex and SGA. Effect modification is analysed by entering an interaction term (SGA*HPC) into the SAS code.

	Height Percentile Change		
	Child Health and Development Studies		
Working Memory Outcome variable	Birth to 4 months	4 months to 1 year	1 to 4 years
	b (sd) *P Value* *N*	*b (sd)* *P Value* *N*	*b (sd)* *P Value* *N*
Verbal Recall	0.28 (0.23) 0.24 154	0.15 (0.31) 0.64 138	0.42(0.28) 0.15 126
Attention With Interference	-0.01 (0.13) 0.97 159	0.61 (0.18) <0.01 143	0.04 (0.16) 0.80 131
Attention	-0.13 (0.10) 0.17 159	0.09 (0.14) 0.50 143	-0.06 (0.12) 0.63 131
Processing Speed	0.11 (0.11) 0.36 157	0.11 (0.16) 0.50 141	0.18 (0.13) 0.17 129
	New England Family Studies		
Verbal Recall	-0.35 (0.17) 0.04 190	0.27 (0.20) 0.17 189	-0.30 (0.20) 0.14 193
Attention With Interference	-0.16 (0.09) 0.08 189	-0.06 (0.11) 0.55 188	-0.07 (0.11) 0.51 192
Attention	0.04 (0.08) 0.59 189	-0.03 (0.08) 0.67 188	-0.07 (0.10) 0.44 192
Processing Speed	-0.12 (0.08) 0.10 189	0.13 (0.09) 0.12 188	0.01 (0.09) 0.95 192

b, beta; *sd*, standard deviation.

Supplemental Table 5. Associations Between a 10% Increase In Height Percentile and Working Memory Outcomes, adjusted for Birth Weight Percentiles. (These associations are based on the fully-adjusted model which includes the covariates age at interview, child race, maternal age, maternal education, maternal height, maternal smoking, parity, sex).

Percentile Height Change Periods	CHDS N	NEFS N
Birth to 4 months	176	204
4 months to 1 year	160	203
1 year to 4 years	149	208

Supplemental Table 6. Chapter 3-Number of Subjects in Study Dataset Groups by Cohort and Growth Period Percentile.

	Percent of Observations with Missing Covariate Data		
	Height Growth from Birth to Age 4 Months	Height Growth from Ages 4 Months to 1 Year	Height Growth from Ages 1 Year to 4 Years
CHDS Subjects	3%-4%	3%-4%	3%-4%
NEFS Subjects	25%-29%	25%-28%	25%-27%

Supplemental Table 7. Chapter 3-Missing Covariates

	Height Percentile Change		
	Child Health and Development Studies		
	Birth to age four months	**Age 4 months To One Year**	**Ages 1 to 4 Years**
	T *b* (*sd*) p value N	**T *b* (*sd*) p value N**	**T *b* (*sd*) p value N**
Lifetime MDD	**1** -0.45 (0.57) 0.43 **2** -0.68 (0.54) 0.20 167	**1** 0.10 (0.50) 0.84 **2** 0.16 (0.48) 0.74 151	**1** -0.19 (0.53) 0.72 **2** -0.22 (0.48) 0.64 139
	New England Family Study		
Lifetime MDD	**1** 0.43 (0.42) 0.31 **2** 0.37 (0.38) 0.32 204	**1** 0.27 (0.40) 0.49 **2** -0.16 (0.41) 0.70 203	**1** 0.57 (0.40) 0.15 **2** -0.20 (0.38) 0.59 208

T, tertile; 1, lowest tertile, 2, middle tertile.
b, estimated beta; *sd*, standard deviation.

Supplemental Table 8. Associations Between an Tertiles of Height Percentile by period, structured by tertiles and Lifetime MDD. Model is adjusted for age at interview, child race, sex, height percentile at the beginning of the height percentile change interval, maternal age, maternal education, maternal height, maternal smoking, parity, family history of mental illness.

	Height Percentile Change		
	Child Health and Development Studies		
Outcome variable	Birth to 4 months	4 months to 1 year	One to 4 years
	OR 95% CI N	*OR 95% CI N*	*OR 95% CI N*
Lifetime MDD	1.02 (0.84, 1.24) 167	1.00 (0.82, 1.32) 151	0.99 (0.80, 1.23) 139
	New England Family Study		
Lifetime MDD	0.98 (0.85, 1.12) 204	0.96 (0.84, 1.10) 203	0.94 (0.80, 1.10) 208

OR, log odds ratio; *CI*, confidence interval.

Supplemental Table 9. Odds Ratios for lifetime MDD Given a 10% Increase in HPC, Adjusted for Birth Weight. Model is adjusted for age at interview, subject race, sex, height percentile at the beginning of the height percentile change interval, maternal age, maternal education, maternal height, maternal smoking, parity, family history of mental illness.

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Methods Appendix

1. <u>Index Groups</u>

The table below lists the sizes of groups by cohort, sex and gestational age expressed in

weeks.

Sex and Gestational Age (weeks)	Number of Subjects CHDS cohort	Number of Subjects NEFS cohort
Male-38	1000	725
Male-39	1870	1332
Male-40	2039	1807
Male-41	1309	1419
Male-42	656	757
Male-43	273	300
Female-38	856	648
Female-39	1712	1255
Female-40	2005	1702
Female-41	1470	1470
Female-42	660	778
Female-43	269	309
Total	14,119	12,502

Table 1.   CHDS and NEFS Cohort Sizes

2. <u>Height Measures and Smoothing Spline Analysis.</u>

Height measurements were obtained from existing data files. Data included birth length and length at approximately 4 months and 1 year and height at 4 years. Exact ages at height measurements were also included in each file. Each file was reformatted as a .csv file and then input to the R statistical program. The height estimates at each age were exported to .csv files.

Below is an example of the R statistical program used for the study analyses. The purpose of this program is to transform the height measurement and age at height measurement for each subject into a height curve from birth to approximately age 4, depending on the subject's age at the last measurement. From this curve, a subject's height at ages 4 months, 1 year and 4 years are estimated.

The major purposes of the code are outlined below and the code follows.
- Lines 1 to 39 is code prepares for the calculation for height curves and formats output. This includes downloading the data file, specifying variables and the smoothing parameter, setting up the growth curve formats.
- Lines 40 to 42 specifies that if there are 2 or less height measures for a subject then a growth curve will not be calculated and the output will be labeled 'N/A'.
- Lines 43 calculates a growth curve for each subject if there are 3 or more height

measures.

- Lines 44 to 45 specifies the estimated heights at ages 4 months, 1 year and 4 year based on the height curves.

- Lines 46 to 50 to puts the estimated heights into the output data set.

- Lines 51 to 53 is formatting code.

R Code

1. library(cobs)

2. data.path="/Users/mkilty/Documents/Dissertation and R/NExcel Source Folder/";

3. result.path="/Users/mkilty/Documents/Dissertation and R/NR Results Folder/";

4. plot.path=result.path;

5. data.name="nefs141c.csv";

6. study="nefs141c";

7. var.m="height";

8. var.id="eid";

9. var.t="age"; #1

10. if(study=="nefs141c"){df.h=1;} #else {df.h=1;}

11. lambda.h=0;

12. extra=100

13. nefs141c=read.table(paste(data.path,data.name,sep=""),header=T,sep=",",na.strings = ".");

14. if(study=="nefs141c"){nefs141c=nefs141c[,c(var.id,var.t,var.m)];}

15. nefs141c=nefs141c[!is.na(nefs141c[,var.m])&!is.na(nefs141c[,var.t])&!is.na(nefs141c[,var.m]),]

123

```
16. nefs141c=nefs141c[order(nefs141c[,var.m],nefs141c[,var.id],nefs141c[,var.t]),]

17. c.eid=unique(nefs141c[,var.id]) ;

18. #changed edah_id to eid;

19. N=length(c.eid);

20. grid1=c(0,4/12,1,4)

21. label1=c("0","4m","1y","4y")

22. xlimh=range(nefs141c[!is.na(nefs141c[,var.m]),var.t],na.rm=T)

23. ylimh=range(nefs141c[,var.m],na.rm=T);

24. grid141=seq(from=0,to=xlimh[141],length.out=100);

25. xgrid1=NULL;

26. xgrid1NA=NULL;

27. xgrid141=NULL;

28. plotname=paste(plot.path,study,var.m,"All.pdf",sep="")

29. pdf(plotname,height=11,width=8)

30. par(mfrow=c(5,3),cex.main=0.8)

31. for (i in 1:N)

32. {eid.h=c.eid[i]

33. nefs141c.here=nefs141c[nefs141c[,var.id]==eid.h,];

34. t.h=nefs141c.here[,var.t];

35. m.h=nefs141c.here[,var.m];

36. plot(t.h,m.h,type="p",xlim=xlimh,ylim=ylimh,pch=1,cex=1,xlab="Time(days),

37. ylab=var.m,main=paste(study," eid=",eid.h,sep=""));

38. abline(v=grid1,lty=141);
```

39. axis(side=3,at=grid1,labels=c("0","4m","1y","4y"));

40. if (length(t.h)<=2){

41. xgrid1.h=data.frame(id=eid.h,T=matrix(rep(NA,length(grid1)),nrow=1));

42. xgrid1=rbind(xgrid1,xgrid1.h); }

43. else{if(length(t.h)==3){smooth.res=cobs(t.h,m.h,constraint="increase",degree=1,la

mbda=lambda.h)}else{smooth.res=cobs(t.h,m.h,constraint="increase",

lambda=lambda.h,degree=df.h);grid141=seq(from=min(t.h),to=max(t.h),length.out=

100);xgrid1.h=predict(smooth.res,grid1)[,2];xgrid141.h=predict(smooth.res,grid14

1)[,2];

44. xgrid1.h[grid1>=(max(t.h)+extra)]=NA;

45. points(grid1,xgrid1.h,pch=2,cex=2);

46. lines(grid141,xgrid141.h,lty=1);

47. xgrid1.h=data.frame(id=eid.h,T=matrix(xgrid1.h,nrow=1));

48. xgrid1=rbind(xgrid1,xgrid1.h);

49. rm(smooth.res) }if (i%%100==0){cat("finish the ",i,"th \n",sep="")}}}

50. dev.off()

51. names(xgrid1)=c(var.id,paste(var.m,label1,sep="_"))

52. write.table(xgrid1,paste(plot.path,study,var.m,"all.csv",sep=""),sep=",",row.names=F

,na=".")

53. save.image(paste(plot.path,study,var.m,"all.RData",sep=""))

3. Calculation of Height Percentiles

The 24 .csv output files were then reformatted into .xls files and imported separately into the SAS statistical program. The Box Cox statistical transformations were accomplished using the PROC TRANSREG function. For each file the PROC TRANSREG function determined an exponent, known as *lambda,* to derive normally distributed values from the input data. These transformed distributions were calculated for 96 files given that there are 24 cohorts and 4 age distributions to be calculated.

Next, the PROC TRANSREG output datasets were input into the PROC STANDARD function. This function transformed the data into values with a mean of '0' and a standard deviation of '1'. These transformed values were then input into the PROC RANK function to determine percentiles from 0 to 99. Height percentile data was exported to an .xls file.

An example of SAS coding for the PROC TRANSREG, PROC STANDARD AND PROC RANK functions is set forth below.

data c138trexmd; set c138trex;

if height_0 = '.' then delete; run;

ods graphics on;

data c138trexz; set c138trexmd;

   z = 0; run;

proc transreg data=c138trexz maxiter=0 nozeroconstant details;

model BoxCox(height_4y/ lambda=-9 to 9 by 0.1) =   identity(z);

output out=c1384trans;run;

Proc standard DATA=c1384trans MEAN=0 STD=1 OUT=c1434;VAR theight_4y;run;

proc rank data=c1434 groups = 1000 out=c1434p;

var Theight_4y; run;

4. <u>SAS Code for Generalized Linear Models</u>-The following SAS code is for a fully adjusted linear model with a continuous outcome variable and a random effects variable, edah_fam to control for family correlations.

```
Proc mixed data=cmerge5 covtest ORDER=formatted;

class edah_fam;

model dig3 = b4mptbirthhtp height_mom_in me white par ageterm_mom smk age_agg sex/
solution;

repeated / type = cs subject= edah_fam r ;

run;
```

The following SAS code is for a fully adjusted linear model with a dichotomous outcome variable and a random effects variable, edah_fam to control for family correlations.

```
proc genmod data=cmerge5 descending;

class edah_fam ; PARAM=REFERENCE REF=FIRST ;

model av = oney4ypnumt ht1p  height_mom_cm me white par

ageterm_mom smk age_agg  /dist=bin link=logit;

repeated subject=edah_fam / type=exch corrw;

run;
```

Both of these models were used in the analyses of the CHDS data.

5. <u>Imputation for Missing Data</u>

The missing maternal height and other covariate data were imputed in the NEFS dataset.

The imputation methods are described below.

1. The imputation data set included all variables in the NEFS fully adjusted model
   including the outcome variable.

2. Other variables from the NEFS dataset were included if they were significantly
   correlated with height_mom_cm but not included in the generalized model. For
   instance, the pre-pregnancy weight variable is correlated with height_mom_cm but
   is not included in the generalized linear model.

3. The imputation process included 20 'iterations' and used a random seed number
   chosen by the website random.org.

4. There are several SAS procedures to impute the missing data and then using
   imputation methods along with the linear mixed models.

   a. The following SAS codes creates new variables to include both future
      imputed data points as well as original NEFS data points. We included
      variables from the linear mixed models used in the analyses as well as other
      variables that are correlated with maternal height since that variable had by
      far the most missing data.

         data nmerge4impute; set nmerge7;

         mother_racei=mother_race;

         incomei=income;

religion_momi=religion_mom;

prepreg_weighti=prepreg_weight;

mei=me;

smki=smk;

sexi=sex;

pari=par;

ageterm_momi=ageterm_mom;

age_aggi=age_agg;

whitei=white;

height_mom_cmi=height_mom_cm;

dig3i=dig3;

oneypi.=oneyp;

oney4ypti=oney4ypt; run;

b. The following SAS code creates imputed values for missing data. After this step, the variables ending in 'i' will include original and imputed data.

```
proc mi data=nmerge4impute seed=413490 nimpute=20
out=nmerge20;
var oney4ypnumti oneypi dig3i mother_racei incomei religion_momi
prepreg_weighti mei height_mom_cmi smki sexi pari whitei
ageterm_momi;run;
```

6. The following generalized linear models are the same as those used for the CHDS dataset but have been modified to incorporate imputation methods. There are 20 imputations of the results for each model. The imputed data points for the covariates but not the exposure or outcome variables are used in the models. The PROC MIANALYZE procedure following each model combines the results of the analyses of imputations and generates valid statistical inferences.

proc mixed data=nmerge4 covtest ORDER=formatted;

 by _imputation_;

 class edah_fam ;

 model irecall= b4mpt zeropi sexi age_aggi ageterm_momi

  WHITEi height_mom_cmi MEi pari smki / solution;

 repeated / type = cs subject= edah_fam r ;

 ods output SolutionF=mxparms; run;

 proc mianalyze parms=mxparms;

 modeleffects intercept b4mpt zerop age_aggi ageterm_momi

 WHITEi height_mom_cmi MEi pari smki sexi; run;

proc genmod data=nmerge21 descending;

by _imputation_;

class edah_fam ; PARAM=REFERENCE REF=FIRST ;

model av = oney4ypt oneyp sex height_mom_cmi mei whitei pari ageterm_momi smki

age_aggi /dist=bin link=logit;

repeated subject=edah_fam / type=exch corrw;

ods output GEEempPest=gnparms;

run;

proc mianalyze parms=gnparms;

 modeleffects intercept oney4ypt oneyp age_aggi ageterm_momi sgai sexi

WHITEi height_mom_cmi MEi pari smki/;run;