Prenatal overnutrition magnifies estimated effects of physical activity on cardiovascular risk

by

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CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

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has been approved

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Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis.

Abstract

Background: Prenatal overnutrition due to maternal obesity or diabetes can induce metabolic and physiologic changes in the fetus that increase the child's risk of developing cardiovascular disease later in life. These changes may also alter the child's physiological response to physical activity. However, few studies have explored the potential interaction between prenatal overnutrition and offspring physical activity as determinants of cardiovascular health.

Objective: We aimed to determine the extent to which children who experienced prenatal overnutrition are more sensitive to the harmful effects of physical inactivity on developing cardiovascular disease later in life.

Methods: We analyzed data from the National Longitudinal Study of Adolescent and Adult Health (Add Health), a nationally representative cohort of US adolescents followed into adulthood (n=20,745) with four data collection waves between 1994 and 2008. The outcome was predicted 30-year cardiovascular disease (CVD) risk in early adulthood (Wave IV), computed by a validated algorithm based on objective cardiometabolic measures. Using gender-stratified multivariable linear regression, we modeled log-transformed 30-year CVD risk as a function of (1) low and high birth weight and (2) self-reported moderate-to-vigorous physical activity (MVPA) frequency in adolescence (Wave I) and young adulthood (Wave III), adjusting for age, smoking, and sociodemographic factors.

Results: Greater MVPA frequency in adolescence was associated with lower predicted 30-year CVD risk in high birth weight (HBW) females (β=-0.018 [95% confidence interval: -0.032, -0.005], p=0.02 for HBW×MVPA interaction) and to a lesser degree in HBW males (β=-0.008 [95% CI: -0.019, 0.003], p=0.09 for HBW×MVPA interaction). In females and males of low birth weight (LBW) or normal birth weight, MVPA frequency in adolescence was not significantly associated with predicted 30-year CVD risk and LBW×MVPA interactions were not significant. In females and males of any birth weight, MVPA frequency in early adulthood was not significantly associated with predicted 30-year CVD risk.

Conclusions: Greater adolescent MVPA was most strongly associated with lower 30-year CVD risk in those who were born HBW, especially HBW females. Children born at HBW may be especially sensitive to the effects of physical activity on reducing risk of cardiovascular disease later in life, with important implications for disease prevention and health policy.

Introduction

Cardiovascular disease is the leading cause of death worldwide, accounting for an estimated 17.5 million deaths in 2012.[1] Adult behaviors such as physical inactivity, poor dietary habits, and smoking are long-established factors that increase the risk of developing cardiovascular disease, and these are a major focus of current individual and population-level interventions. Recently, however, interest has grown in the role that developmental factors may play in the pathogenesis of cardiovascular disease and other chronic diseases.

The developmental origins of health and disease (DOHaD) hypothesis first proposed by David Barker posits that adverse conditions in early life can predispose a person to chronic diseases such as heart disease, diabetes, and obesity later in life.[2] A large and accumulating body of epidemiologic and biological research supports and extends Barker's hypothesis. This evidence suggests that maternal health during the prenatal period in particular can affect fetal development, altering physiology in ways that increase future risk of cardiometabolic diseases.[3] In addition to ongoing research into genetic and environmental mechanisms, a growing understanding of epigenetics has shed light on the pathophysiology underlying developmental programming. Epigenetic processes, including DNA methylation and histone modification, can result in lasting changes to gene expression that are transmitted to offspring without changes in the DNA sequence.[4] Other mechanisms occurring in early life may also contribute to cardiovascular disease (CVD) risk, including abnormal organ development, fetal hormonal imbalances (e.g., glucocorticoid overexposure, dysregulation of the renin-angiotensin system, elevated leptin and insulin), oxidative stress, and sex-specific effects.[5,6]

Early studies by Barker and others focused on fetal undernutrition as the initial insult ("first hit") that programs the fetus for adult disease.[2,7,8] Low birth weight (LBW), a marker for fetal undernutrition and intrauterine growth restriction, has been associated with hypertension, insulin resistance, coronary heart disease, renal disease, and diabetes.[9–14]

Prenatal overnutrition and cardiometabolic risk

With obesity and type 2 diabetes mellitus becoming increasingly prevalent worldwide, fetal overnutrition is a relatively new avenue for research to expand understanding and suggest new preventive interventions. Overnutrition is a form of malnutrition in which major nutrients are supplied in excess of amounts required for normal metabolism, and is generally associated with maternal obesity and maternal diabetes. High birth weight (HBW) is a result of and indicator for prenatal overnutrition.[15]

A large body of literature supports an association between high birth weight and later obesity.[16–18] Interestingly, several studies have found elevated adult diabetes risk in those born at low birth weight (<2.5 kg) and in those born at high birth weight (generally >4 kg); that is, a U- or J-shaped relationship between birth weight and risk of diabetes.[13,19] With regard to cardiovascular disease, there is conflicting evidence. Many large observational studies have shown a generally inverse relationship between birth weight and CVD,[9,20–23] despite the associations of HBW with diabetes and obesity, which are CVD risk factors. However, high birth weight is a heterogeneous category that includes physiologically and developmentally normal babies, especially in older cohorts that predate the current epidemic of obesity and type 2 diabetes; relatively few studies with long-term follow-up have assessed cohorts born since the rise of these diseases. Therefore, it is possible that disease associations with HBW may be fundamentally different in contemporary populations.

A recent prospective study found that children born large for gestational age who displayed accelerated postnatal growth had higher blood pressure at five years of age.[24] In a study of a Canadian pediatric population, a positive association was found between high birth weight and diastolic blood pressure.[25] High birth weight has been associated with atrial fibrillation[26,27] and carotid intimal media thickness.[17] A meta-analysis of 31 studies found that HBW was associated with higher systolic and diastolic blood pressure in childhood but lower blood pressures in adulthood.[28] Other recent studies have not found significant associations between HBW and later CVD risk.[29,30] However, research examining prenatal overnutrition and cardiovascular outcomes in US populations has been limited. To date there have been no large-scale cohort studies, and none in adolescents or young adults.

Physical activity and cardiometabolic risk

It is well established that physical activity is a key behavioral determinant of cardiovascular health, being linked to lower risk of heart disease and stroke.[31] Moderate-intensity exercise is associated with lower risk of type 2 diabetes in prospective studies.[32] Studies of children and adolescents using objective measures of physical activity have linked higher physical activity levels and cardiorespiratory fitness with lower adiposity[33] and metabolic risk.[34] Moreover, adolescence and young adulthood represent a pivotal period for primary prevention of cardiovascular disease, as lifelong behavioral patterns are established that prevent or promote obesity, insulin resistance, and hypertension.[35]

Interaction between physical activity and prenatal overnutrition

Emerging evidence indicates that the long-lasting effects of excess nutrition in the intrauterine period may be modified by physical activity, diet, and

other behaviors long after birth. Given what is known about traditional cardiovascular risk factors,[36] developmental and behavioral factors together may have an additive or even multiplicative effect on CVD risk (**Figure 1**). Recent studies in animals and in humans have explored the potential interaction between physical activity level and early life stressors as determinants of cardiometabolic health. In laboratory experiments, improvements in metabolic measures have been reported in exercised versus sedentary rats born to obese dams.[37,38]

Several human studies have explored the potential interaction between physical activity level and developmental factors as determinants of cardiometabolic health. In studies of middle-aged and elderly populations, low cardiorespiratory fitness and physical activity levels were found to strengthen the association of small birth size with metabolic syndrome[39] and type 2 diabetes.[40] In adolescents, weaker estimated effects of low birth weight on serum leptin[41] and on insulin resistance[42] were observed in those with greater physical activity. All four studies had European populations and relatively modest sample sizes. With respect to high birth weight, the analogous question is whether those who experienced overnutrition *in utero* are more sensitive to the salutary effects of physical activity later in life. A recent cross-sectional study found that the effect of HBW on obesity in adolescents was mitigated by greater physical activity, especially in girls.[43] Other studies have not found evidence that physical activity or fitness moderates the association between birth weight and metabolic risk.[44]

None of these prior studies assessed CVD-specific outcomes. Further, none used longitudinal design with prospective assessment of outcomes after physical activity exposures; all assessed physical activity and outcomes of interest at a single time. Therefore, we undertook the first study examining longitudinal associations of birth weight and physical activity on later cardiovascular risk in a large, nationally representative prospective cohort.

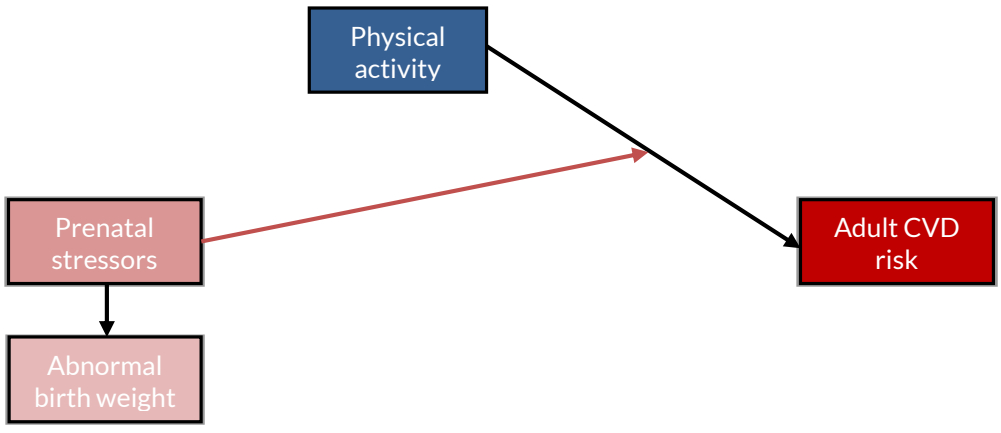

Figure 1. Directed acyclic graph of hypothesized relationships

Objectives

Our principal aim was to determine the extent to which birth weight modifies the estimated effect of physical activity on adult cardiovascular risk. We hypothesized that children who experienced prenatal overnutrition or undernutrition are more sensitive to the harmful effects of physical inactivity on developing cardiovascular disease later in life, and therefore that physical activity is more strongly associated with lower 30-year CVD risk in participants who had high or low birth weight.

Methods

Source data

We examined existing data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative cohort of 20,745 US adolescents followed into adulthood.[45] The primary purpose of Add Health is to study how environments and behaviors in adolescence affect health and academic and career achievement outcomes in young adulthood. Four "waves" of in-home interviews were conducted between 1994 and 2008, collecting data on socioeconomic, family, community, psychological,

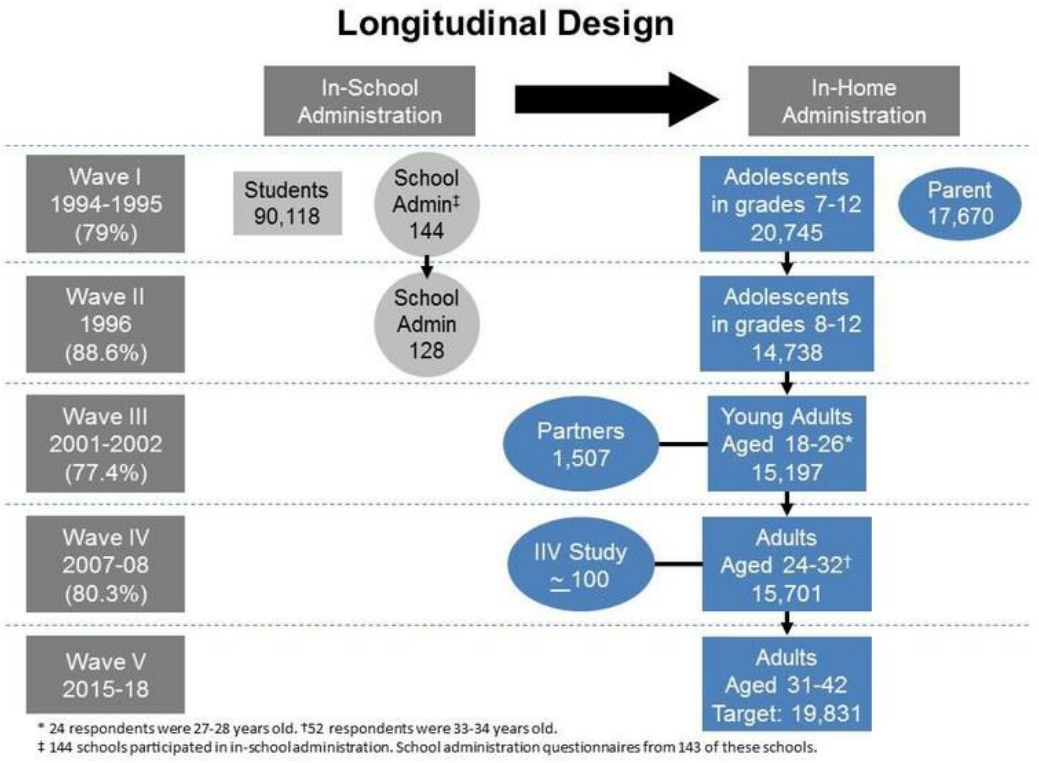

Figure 2. Add Health study design schematic

and health factors (**Figure 2**). Data were collected from participants, parents, school administrators, siblings, and friends. Waves I and II represent the adolescent period, whereas Wave III and Wave IV represent young adulthood. Wave IV additionally included collection of clinical data from participants.

Participants

Selection criteria and sample design in Add Health

Add Health's target population was all adolescents in the United States who were in grades 7–12 in 1994–95. The study employed a school-based clustered sampling design. From a sampling frame of 26,666 US high schools, 80 high schools and their feeder schools were selected using randomization that weighted each school according to its size. The final sample included 145 schools in 80 communities, comprising more than 100,000 adolescent students. Full details of the Add Health design are available on the study web site.[46]

From this group, 90,118 students completed an in-school questionnaire for the first stage of Wave I (1994–95). These respondents were then stratified according to sex and grade and a core sample was selected (n=12,105), with roughly equal individual-level and school-level sample sizes for each of the 12 strata (six grades and two sexes). Supplemental samples were drawn based on responses to the in-school survey for several special groups (Cuban, Puerto Rican, or Chinese ethnicity; and blacks having a parent with a college degree), adoption status, and disability. Sampling weights were applied to create an overall sample that was representative of the US population of adolescents at baseline. During the second stage of Wave I, participants in the core and supplemental samples (n=20,745) and their parents were interviewed in their home as described in the following section on data collection.

All adolescents who were initially in grades 7–11, as well as 12th graders in the genetic sample and adopted sample were re-interviewed at home approximately one year later for Wave II (1996, n=14,738). Wave III (2001–2; n=15,197) consisted of in-home interviews with Wave I respondents, then aged 18–26, who could be located, as well as their partners. Wave IV (2008–9) also consisted of in-home interviews with Wave I respondents, then aged 24–32, who could be located; 80.3% participated, resulting in a sample size of 15,701. In Wave IV, biomarkers and other clinical data were obtained from participants in addition to a new in-person questionnaire as described below.

Participant recruitment and consent

No new participants were recruited for our study. All data use was in compliance with the Add Health restricted-use data contract. The research was determined to be exempt from 45 CFR 46 regulations by the Institutional Review Board of Oregon Health & Science University.

Selection criteria and sample design for the current study

Starting with all participants in the core and supplemental samples (**Figure 3**), we excluded 7740 participants who did not participate in Waves I, III, and IV because of the key variables drawn from each of these waves. We also excluded those who were pregnant at Wave IV (n=446) because we anticipated that physiologic changes of pregnancy would interfere with interpretation of associations. We then excluded participants who were missing any component of the 30-year CVD risk prediction algorithm (n=1822) because construction of the outcome variable required all of these (age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status at Wave IV, hypertension medication status at Wave IV, and diabetes mellitus status at Wave IV). Finally, we excluded participants missing moderate-to-vigorous intensity physical activity (MVPA) (n=31), birth weight (n=2152), race/ethnicity (including "other" race) (n=104), or smoking status at Wave I or III (n=39).

Single hot deck imputation was used to replace missing data for household income at Wave I and parental educational attainment at Wave I; thus, there were no participants excluded for missing data for these variables. Imputation is a means of avoiding selection bias that can be introduced by listwise deletion of participants with any missing data. Hot deck imputation is technique that replaces missing values for a particular participant with observed values from another, randomly selected participant with complete data.[47] The `hotdeck` module for Stata was used with the following syntax: `hotdeck [education variable] [income variable]`.[48]

A final total of 8440 participants remained in our analytic sample. Our use of sample weights reduced the impact of losses to follow-up by weighting the remaining participants to be representative of the target population. Compared with participants who were excluded from analysis, those who were included were more likely to be female, be white, be smokers at Wave III, and have parents who attended college; those included were also slightly younger and had a slightly lower predicted 30-year CVD risk. These differences were generally minor and expected. Notably, missingness was unrelated to MVPA at Wave I or Wave III or birth weight category.

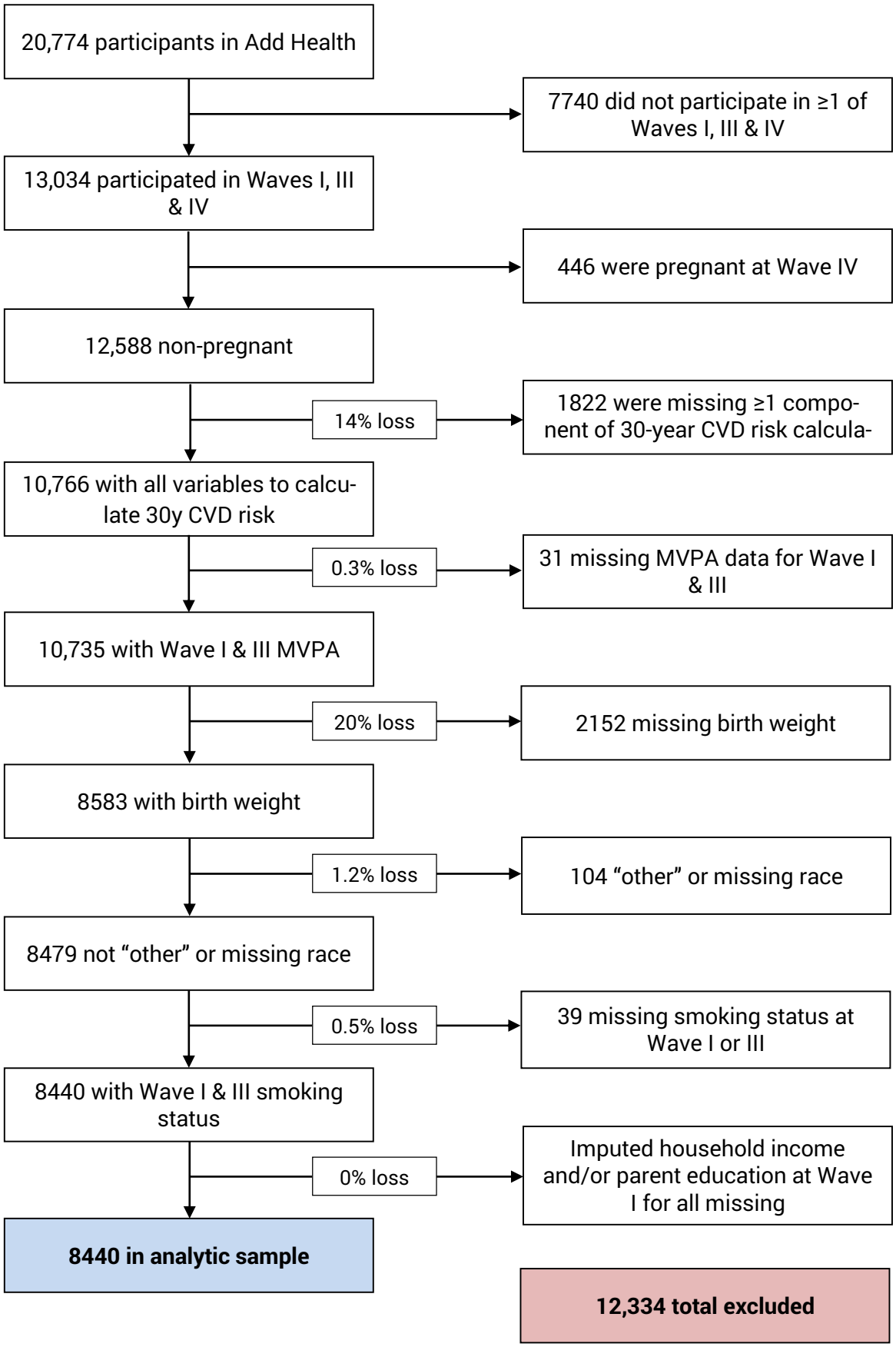

Figure 3. Inclusion and exclusion criteria for analytic sample

Data collection

Add Health questionnaires

At each data collection wave of Add Health, participants were asked to respond to questions on topics such as health status, psychological status, socioeconomic status, nutrition, behaviors, environmental context, health-facility utilization, family and peers, and drug use. The majority of interviews took place in participants' homes. An interviewer asked questions and entered participants' responses into a computer for less sensitive sections of the questionnaire, whereas participants used an audio computer-assisted self-interview for more sensitive sections to improve the reliability of self-reported information.

Wave I (1994–95) included a parental questionnaire on demographic and health information about themselves and their adolescent child, including birth weight of the participant and parental diabetes and obesity at the time of the interview.

Blood pressure and blood specimens

In Wave IV of Add Health, trained and certified field interviewers used appropriately sized blood pressure cuffs and automatic monitors to measure blood pressure. Systolic and diastolic blood pressure were measured (mm of mercury) after the participant had rested at least five minutes in the seated position, with three serial measurements at 30-second intervals. In Add Health, the final measures were constructed as the average of measures 2 and 3 (98.8% of analytic sample). If either measure 2 or 3 was missing, the other single measure was used (0.8% of analytic sample). In cases where both measures 2 and 3 were missing, measure 1 was used (0.4% of analytic sample).

Field interviewers also collected dried capillary whole blood spots via finger prick and applied to blood collection cards, which were sent to an external lab for processing. Blood assays included lipid profile, measured by colorimetric and fluorimetric assays (mg/dL)[49], and hemoglobin A1c, measured by turbidimetric inhibition immunoassay (percent).[50]

Study variables

Outcome

We selected the 30-year cardiovascular disease (CVD) risk prediction algorithm developed by Pencina et al. as our outcome variable.[51] This algorithm quantifies overall cardiovascular health using a panel of established cardiovascular risk factors, and is derived from the Framingham Offspring cohort, whose participants were followed prospectively from baseline examination in 1971–74 for a median of 32 years.[52] Data from participants aged 20–59

years (n=4506) were used to create the algorithm. The strengths of this algorithm are that it is derived from a seminal longitudinal study of cardiovascular outcomes in a United States population, it includes a younger age group than most other cardiovascular risk scoring systems, it accounts for the competing risk of non-cardiovascular death, it was internally validated as a good predictor of long-term cardiovascular risk, and it is compatible with a combination of continuous and categorical risk factors.

Because the absolute incidence of cardiovascular events is very low in young adults, analysis of associations with a CVD event-based outcome would be difficult. Using predicted CVD risk as an outcome instead allows adequate statistical power to establish associations. Moreover, because this algorithm predicted a range of CVD events, it should capture more of those at risk than would a single component (e.g., blood pressure).

We used the "full CVD" algorithm of Pencina et al., which predicts 30-year risk of coronary death, myocardial infarction, fatal or non-fatal stroke, coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication, or congestive heart failure. The algorithm uses age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, diabetes status, and hypertension medication status as inputs. Although the outcome variable is computed as a percentage (estimated percent risk of CVD over the ensuing 30 years), it is not a measure of counted events per unit time; the risk of CVD is essentially a scoring system with a scale of 0 to 100. The range in our sample was 1 to 59.

Age was measured at the time of the Wave IV questionnaire and ranged from 24–34. We constructed the variable using the formula (interview month & year) – (self-reported month & year of birth). Only 52 respondents in our sample were 33 or 34 years old at the time of interview; these were recoded to age 32 to reduce imprecision at the upper end of the distribution.

Sex was derived from self-reported gender at Wave IV or the most recent wave for which the participant reported a gender. Add Health did not record transgender status, but in the analytic sample four subjects reported male gender at Wave I and female gender at subsequent waves, and three subjects reported female gender at Wave I and male gender at subsequent waves.

Systolic blood pressure (SBP) was measured as a continuous variable at Wave IV using the constructed variable from Add Health as described above.

Total cholesterol (TC), an estimate of circulating cholesterol bound to all lipoproteins, was measured from finger prick blood samples at Wave IV as described above.

High-density lipoprotein cholesterol (HDL-C), a measure of circulating anti-atherogenic particles, was measured from finger prick blood samples at Wave IV as described above.

Unlike low-density lipoprotein cholesterol (LDL-C), TC and HDL-C do not require a fasting blood sample. Many studies have shown that non-HDL-C (TC minus HDL-C) is equal or superior to LDL-C as an estimate of cardiovascular event risk.[53–55] Due to concerns about limited precision, Add Health reported deciles for TC and HDL-C rather than absolute values, so we converted deciles of these variables to median values of deciles derived from NHANES 2007–8 and 2009–10 participants **(Appendix Table A1**), because absolute values were required by the risk prediction algorithm.[56,57]

Smoking status: We constructed a binary variable that defined current smoking at Wave IV as ≥ 1 cigarette per day on each of the previous 30 days. Numerous studies have demonstrated a large increase in CVD risk with even one cigarette per day.[58–61]

Diabetes status: We used the constructed variable C_JOINT from Add Health to assign diabetes status. This variable classified participants as having diabetes if they met one or more of the following criteria: Hemoglobin A1c (HbA1c, glycated hemoglobin) of ≥ 6.5%, fasting glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, self-reported history of diabetes except during pregnancy, or self-report of using anti-diabetic medication in the previous four weeks.

Hypertension medication status: We constructed a binary variable based on self-reported prescription medication use in the previous four weeks at Wave IV. As part of the Add Health Wave IV interview, a trained interviewer looked up each reported medication in a medication information and classification database (Multum Lexicon™, Cerner Multum, Inc.; Denver, Colo.) We included codes for medication classes that are used to treat hypertension; these are listed in **Appendix Table A2**.

Primary exposures

Physical activity at Wave I and **Wave III** were our primary exposure variables. These were measured as self-reported weekly frequency of moderate-to-vigorous intensity physical activity (MVPA), such as skating and cycling, fitness exercise, or active sports, using a standard, interview-administered activity recall based on self-report questionnaires that have been validated in other epidemiologic studies.[62] Participants were in grades 7–11 at Wave I (1995) and aged 18–26 at Wave III (2001–2). Because of the typically different life situations between middle/high school and young adulthood, we expected significant intraindividual changes in MVPA frequency from Wave I to III. Given the similarity of these two variables, we checked for correlation

and collinearity as detailed in the statistical analysis section below. Because of changes in Add Health's physical activity questions between waves, Wave III MVPA (33 activities per week maximum) was scaled to make it comparable to Wave I MVPA (16.5 activities per week maximum) by multiplying by (16.5/33), as other researchers have done.[63,64]

Original survey questions from which these variables are derived, including a list of activities asked in the questionnaire, are listed in **Appendix Table A3**.[65]

Effect modifiers

Birth weight of adolescent participants was assessed in the parent interview during Wave I and recorded to the nearest ounce. We used clinically relevant thresholds for low and high birth weight that have been used in many prior studies: Low, <2.5 kg (5 lb, 8 oz); Normal, 2.5–4 kg; High, >4 kg (8 lb, 13 oz).

Gender is an established risk factor for cardiovascular disease; males have significantly higher risk but also tend to be more physically active. Our method of variable construction is detailed in the Outcome section above. Given the potential for interactions between gender and other factors, we stratified all analyses by gender. Gender differences in developmental programming-related effects and gender interactions have been reported in many studies and have biological plausibility.[43,66–68]

Potential confounders

We considered the following variables to be potential confounders because they were likely to be associated with the primary exposures (physical activity) and the outcome (cardiovascular risk).

Age is an established risk factor for cardiovascular disease and tends to be inversely correlated with physical activity. Wave IV age was used; see above for details of variable construction. Although Wave IV age was a component of the algorithm used to create the outcome variable (predicted CVD risk), including it separately as a covariate was important to adjust for its expected confounding effect, as it is clearly associated with both the primary exposures and the outcome. Because age is independently associated with physical activity, it should be included as a confounder; the CVD risk algorithm does not itself include physical activity. Moreover, model building revealed age to be an empirical confounder, as removal of age from the full model resulted in substantial changes in the coefficient for MVPA at Wave I in gender and birth weight-stratified models and lesser but still large (>10%) changes in the coefficient for MVPA at Wave III.

Smoking is an established risk factor for cardiovascular disease and is associated with lower physical activity.[69] Because smoking status at Wave IV was

included in the composite outcome variable, it was not included as a covariate in the regression model. Instead we included smoking status at Waves I and III because they were expected to be associated with MVPA at Waves I and III; these were constructed as binary variables in the same way as Wave IV smoking, described above.

Race/ethnicity is correlated with social and environmental determinants of health and disease. In broad terms, non-whites and Hispanics are more likely to experience socioeconomic adversity and also tend to have higher risk of cardiovascular disease. Differences in physical activity level by race/ethnicity have also been reported.[70] We constructed a categorical race/ethnicity variable using self-reported race or ethnicity. All Hispanics were coded as Hispanic, and remaining participants were categorized as white, black, Asian, or other.

Education level is a socioeconomic factor that is associated with both cardiovascular disease and physical activity. Assessing educational attainment early in adulthood (e.g., Wave III, ages 18–24) poses problems as many people do not complete their education until later in their 20s or 30s. As parental education is generally considered a good predictor of offspring education, we used self-reported educational attainment of participants' parents at Wave I. We constructed a categorical variable with three levels: no college, some college, and college degree or higher. Hot deck imputation was used to replace missing data for this variable.

Household income is a socioeconomic factor that is associated with both cardiovascular disease and physical activity. Household income was reported on the parent survey at Wave I and entered as a continuous variable. Hot deck imputation was used to replace missing data for this variable.

Statistical analysis

Statistical analysis was performed with the software package Stata version 13.1 (StataCorp, College Station, Texas). Where possible, analyses were conducted using established survey procedures with sample weights to adjust for the clustered sampling design of Add Health. This ensured that estimates were nationally representative and not biased by the clustered sampling or unequal selection probabilities. In Stata, we identified the survey design characteristics with the `svyset` command and use the `svy` prefix for data analysis commands. Per Add Health guidelines, we used the cross-sectional sampling weight for the wave from which the outcome variable is drawn (GSWGT4_2), rather than a longitudinal sampling weight.[71] We stratified all analyses by gender given the high potential for gender-early-life and gender-behavioral interactions, as noted above.

Descriptive analysis

We conducted descriptive analyses within strata defined by cross-classifications of gender and birth weight category.

Univariate analyses were conducted within each stratum to characterize the data. For continuous independent variables this included mean, standard deviation, distribution, and extreme values; for categorical independent variables this included tabulation and cell counts. As stratification exacerbates problems of sparse data and because high and low birth weight are relatively uncommon, checking cell sizes and missing data was important to ensure adequate numbers for analysis.

One of the assumptions of linear regression is that the dependent variable has a normal distribution. We assessed the distribution of the outcome variable using `gladder` in Stata in order to display histograms of several transformations according to the ladder of powers. The outcome was not normally distributed; a natural logarithm transformation achieved an approximately normally distributed dependent variable for linear regression analysis (**Appendix Figure A1**).

Bivariate descriptive analyses were performed for variable pairs (dependent variable with each independent variable) to assess unadjusted associations, determine unweighted cell sizes, and identify non-comparable distributions. This included cross-tabulation, correlation matrices, and *t*-tests as appropriate for each pair of variables.

Regression analysis

We modeled predicted 30-year cardiovascular disease (CVD) risk as a function of moderate-to-vigorous physical activity (MVPA) at Waves I and III, birth weight category as an effect modifier, and confounders using gender-stratified multivariable linear regression. While our data for independent variables were drawn from repeated measures in Waves I, III, and IV, our dependent variable was measured at Wave IV only; therefore our statistical models were not longitudinal models as there were no repeated outcome measures or follow-up period during which the outcome was assessed.

First, we calculated crude associations between the independent variables (including the primary exposures) and the outcome variable, stratified by gender and birth weight. However, because behavioral exposures are typically highly confounded, the utility and interpretability of the crude associations was limited.

We modeled continuous independent variables (age at Wave IV, MVPA at Wave I, MVPA at Wave III, and household income at Wave I) as linear terms

in the final model based on the results of linearity assessments of their relationships with the outcome in gender- and birth weight-stratified, crude models. Each continuous independent variable was modeled both linearly and categorized into quintiles; coefficients were graphed and assessed visually. Grand-mean centered variables were created from the independent variables and then higher order transformations were applied, tested for statistical significance, and graphed. Though they do not fully accommodate complex survey data, `lowess` and `nlcheck` were run on each crude association and further supported the linearity assessments.

Spearman's rank correlation coefficients between the primary exposure variables (MVPA frequency at Wave I and at Wave III) were 0.22 and 0.24 within females and males, respectively; the variance inflation factor (VIF) for these variables ranged from 1.41 to 1.48. These indicate that the MVPA variables are not highly correlated and have an acceptably low degree of collinearity.

Second, we used multivariable linear regression analyses to model predicted 30-year cardiovascular risk as a function of self-reported weekly frequency of MVPA at Wave I and at Wave III, birth weight category (low, normal, high), and interactions between birth weight category and each of the MVPA variables. A separate analysis (model) was conducted for each of the two genders. Interaction terms between the two physical activity measures or all three independent variables were not included. Because birth weight was categorized into three levels, two binary indicator (dummy) variables were used for LBW and HBW; other categorical variables with more than two levels were also coded with indicator variables. The following *a priori* confounders (controls) were included in the models: age, race, smoking, parental education level, and household income. These fully adjusted models improve comparability with the literature on associations between physical activity and cardiovascular outcomes, which typically adjusts for these variables. The regression model for each gender was defined as follows:

$$\ln(\text{CVD risk}) = \beta_0 + \beta_1(BW_{low}) + \beta_2(BW_{high}) + \beta_3(MVPA_1) + \beta_4(MVPA_3) + \beta_5(BW_{low}\times MVPA_1) + \beta_6(BW_{low}\times MVPA_3) + \beta_7(BW_{high}\times MVPA_1) + \beta_8(BW_{high}\times MVPA_3) + \beta_k[\text{covariates}] + \varepsilon$$

In Stata, the `lincom` function was used to aid interpretation of interaction coefficients by calculating gender- and birth weight-specific associations between each of the two MVPA variables and log-transformed CVD risk.

In order to quantify confounding by each *a priori* confounder and confirm that their inclusion did not affect model precision, we conducted an empirical confounding assessment. Starting with the full, gender-stratified models, we employed the following process for both models:

1. We fitted the fully adjusted model, including the interaction terms specified above, stratified by gender.
2. We performed an empirical confounding assessment of each control variable (listed in Table 1) by removing each individually from each of the full models. We evaluated potential confounders by comparing crude and adjusted birth weight-specific regression coefficients for the primary exposures ($MVPA_1$ and $MVPA_3$); if removal of a variable changed either the $MVPA_1$ or $MVPA_3$ coefficients by at least 10%, it was considered a confounder.
3. Next, we cumulatively removed covariates that were not confounders. Starting with the full model, we removed the weakest confounder found in Step 2 (i.e., that which yielded the smallest percent change in the coefficients for the primary exposures). We then removed the next weakest confounder, proceeding until the coefficients for either primary exposure changed by more than 10%, compared to the full model. The precision of each estimate was assessed by the width of its 95% confidence interval.

Empirical confounding assessment yielded the confounders shown in **Table 1**. Exclusion of variables that did not meet the 10% criterion for confounding did not significantly affect the precision of the main exposure associations, represented by width of the 95% confidence interval for the regression coefficients for $MVPA_1$ and $MVPA_3$. Therefore, we left all variables in the models.

Table 1. Empirical confounders by gender and birth weight category

	Females			Males		
	NBW	HBW	LBW	NBW	HBW	LBW
age (Wave IV)	•	•	•	•	•	•
race	•		•		•	
smoking (Wave I)		•		•	•	
smoking (Wave III)	•	•	•	•	•	•
education (Wave I)	•	•	•	•	•	•
income (Wave I)	•	•	•	•	•	•

The regression coefficients for $MVPA_1$, $MVPA_3$, LBW, HBW, and related interaction terms in the final gender-stratified models were used to estimate effect sizes by birth weight category and gender.

Main effects were considered statistically significant if the two-sided p-value was less than 0.05. Statistical significance of the interactions was assessed at $p<0.10$.

Model diagnostics

We assessed potential multicollinearity between independent variables using the variance inflation factor (VIF) in the final models. Maximum VIF values were 3.88 and 4.99 and mean VIF values were 1.99 and 2.21 for females and males, respectively. A maximum VIF of less than 10 is generally considered acceptable, so we concluded that collinearity was not a concern in our models.

We performed residual analysis with plots of raw, standardized, and studentized residuals, which confirmed the linearity, independence, and homoscedasticity (constant variance) assumptions of linear regression. Q–Q plots of residual versus fitted values confirmed normality of the dependent variable given any fixed values of the independent variables. Shapiro-Wilk, Shapiro-Francia, and skewness tests suggested non-normality of the residuals ($p<0.05$ for all), but this is common with large sample sizes even if the distribution deviates only mildly from normal. Finally, we tested Cook's distance on unweighted data and found no influential points (outliers).

Statistical software packages including Stata 13.1 are currently very limited in supporting model diagnostics using survey weights; therefore, except for raw residual and Q–Q plots, model diagnostics were performed without accounting for survey weighting.

Results

Descriptive statistics

Participant characteristics are summarized in **Table 2.** More males than females were in the high birth weight (HBW) category (14.4% vs. 9.4%, $p<0.0005$). In both genders, LBW was more prevalent among blacks and Asians and those of lower education and household income. Conversely, HBW was more prevalent among whites and Hispanics, and those of higher education and household income. The socioeconomic relationships were stronger in females than in males. Compared to NBW and HBW males, LBW males had a greater proportion of smokers at Wave I and Wave III. Across strata of birth weight by gender, there were no significant differences for MVPA at Wave I or III.

Table 3 shows participant characteristics for variables on which the outcome algorithm predicting CVD risk is based. At Wave IV, LBW females had a significantly higher proportion of diabetes and higher mean predicted 30-year CVD risk. Within each gender, across strata of birth weight, there were no significant differences for smoking status, systolic blood pressure, total or HDL cholesterol, or hypertension medication use at Wave IV.

Table 2. Participant characteristics by gender and birth weight category

	Females			Males		
	NBW	**HBW**	**LBW**	**NBW**	**HBW**	**LBW**
Count [%, unweighted]	3,573 (78.4)	427 (9.4)	559 (12.3)	2,918 (75.2)	560 (14.4)	403 (10.4)
Age, Wave IV mean (SE)	28.0 (0.1)	28.2 (0.2)	28.2 (0.2)	28.2 (0.1)	**28.4 (0.1)**	28.2 (0.2)
Race/Ethnicity [%]						
White	**81.2%**	**11.4%**	**7.4%**	**75.1%**	**18.6%**	**6.3%**
Black/African-American	**79.2%**	**5.1%**	**15.7%**	**75.6%**	**11.0%**	**13.4%**
Asian/Pacific Islander	**76.3%**	**9.0%**	**14.6%**	**86.4%**	**5.8%**	**7.8%**
Hispanic/Latino	**77.0%**	**13.2%**	**9.8%**	**74.5%**	**14.5%**	**11.1%**
Parent's Highest Education, Wave I [%]						
No college	**47.1%**	**42.6%**	**62.1%**	47.0%	44.2%	52.6%
Some college	**19.3%**	**20.3%**	**18.2%**	19.9%	21.8%	17.1%
College degree or higher	**33.6%**	**37.2%**	**19.7%**	33.1%	34.0%	30.3%
Household income ×$1000, Wave I mean (SE)	48.0 (1.8)	47.3 (2.1)	36.0 (2.1)	45.3 (1.6)	49.5 (2.9)	40.7 (2.8)
Smoker, Wave I [%]	11.2%	11.2%	9.5%	**9.3%**	**10.1%**	**12.9%**
Smoker, Wave III [%]	23.5%	27.1%	23.5%	**27.2%**	**27.8%**	**29.9%**
Smoker, Wave IV [%]	22.7%	25.0%	25.2%	27.3%	28.2%	25.4%
MVPA weekly frequency						
Wave I mean (SE)	5.8 (0.1)	5.7 (0.2)	5.4 (0.4)	7.4 (0.1)	7.3 (0.2)	7.5 (0.5)
Wave III [normalized] mean (SE)	2.4 (0.1)	2.7 (0.2)	2.5 (0.2)	3.2 (0.1)	3.2 (0.1)	3.6 (0.3)

Bold text indicates $p<0.05$; pairwise comparison with NBW as referent for continuous variables; χ^2 test for any difference for categorical variables. NBW: normal birth weight. HBW: high birth weight. LBW: low birth weight. MVPA: moderate-to-vigorous physical activity. CVD: cardiovascular disease.

Table 3. Component variables of predicted 30-year CVD risk algorithm by gender and birth weight

	Females			Males		
	NBW	**HBW**	**LBW**	**NBW**	**HBW**	**LBW**
Count [%, unweighted]	3,573 (78.4)	427 (9.4)	559 (12.3)	2,918 (75.2)	560 (14.4)	403 (10.4)
Age, Wave IV mean (SE)	28.0 (0.1)	28.2 (0.2)	28.2 (0.2)	28.2 (0.1)	**28.4 (0.1)**	28.2 (0.2)
SBP, Wave IV mean (SE)	120.8 (0.3)	120.2 (0.8)	121.2 (1.0)	130.7 (0.3)	129.3 (0.8)	130.7 (0.9)
Total cholesterol, Wave IV mean (SE)	186.8 (1.1)	182.6 (2.4)	186.0 (2.5)	188.6 (1.0)	186.6 (2.7)	188.7 (3.2)
HDL cholesterol, Wave IV mean (SE)	54.3 (0.4)	54.3 (1.0)	53.3 (1.0)	49.0 (0.4)	48.3 (0.7)	48.6 (1.1)
Hypertension medication, Wave IV [%]	4.4%	5.8%	3.2%	3.8%	4.5%	6.9%
Diabetes, Wave IV [%]	5.9%	5.4%	**10.8%**	6.2%	5.7%	6.4%
Smoker, Wave IV [%]	22.7%	25.0%	25.2%	27.3%	28.2%	25.4%
30-year CVD risk %, Wave IV, mean (SE)	6.8 (0.1)	6.8 (0.3)	7.5 (0.4)	12.1 (0.2)	12.1 (0.4)	12.2 (0.6)

Bold text indicates $p<0.05$; pairwise comparison with NBW as referent for continuous variables; χ^2 test for any difference for categorical variables. NBW: normal birth weight. HBW: high birth weight. LBW: low birth weight. CVD: cardiovascular disease.

Table 4. Selected component variables of algorithm by quartile of predicted CVD risk, by gender

	Females				Males			
	Quartiles of predicted CVD risk				Quartiles of predicted CVD risk			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SBP [mmHg], Wave IV mean (SE)	114.8 (0.3)	**121.9 (0.5)**	**125.1 (0.6)**	**133.0 (1.0)**	117.8 (1.0)	**124.6 (0.6)**	**128.7 (0.4)**	**135.3 (0.5)**
Total cholesterol [ng/dL], Wave IV mean (SE)	176.3 (1.3)	**188.6 (1.4)**	**193.5 (1.8)**	**205.0 (3.1)**	152.4 (3.0)	**173.5 (2.0)**	**186.5 (1.4)**	**199.0 (1.5)**
HDL cholesterol [ng/dL], Wave IV mean (SE)	59.1 (0.5)	**52.7 (0.6)**	**49.0 (0.7)**	**48.1 (1.1)**	59.1 (1.6)	**54.4 (0.8)**	**49.6 (0.6)**	**45.1 (0.5)**
Hypertension medication, Wave IV [%]	**0.6%**	**1.4%**	**8.5%**	**19.8%**	**0.0%**	**0.0%**	**1.1%**	**8.7%**
Diabetes, Wave IV [%]	**0.2%**	**3.1%**	**8.6%**	**33.1%**	**0.0%**	**0.4%**	**1.1%**	**13.0%**

Quartiles are defined from pooled sample of both genders. Bold text indicates $p<0.05$; pairwise comparison with Q1 as referent for continuous variables; χ^2 test for any difference for categorical variables. MVPA: moderate-to-vigorous physical activity. SBP: systolic blood pressure. HDL: high density lipoprotein. CVD: cardiovascular disease.

Table 4 displays variables that are inputs of the risk prediction algorithm with quartiles of the algorithm output (predicted 30-year CVD risk). Diabetes, blood pressure, and hypertension medication track most closely with predicted CVD risk.

Table 5 shows means and proportions of participant characteristics by quartile of predicted 30-year CVD risk. Predicted risk was generally higher in males than females, as expected based on the algorithm, which assigned higher risk for male gender. In both genders, neither race/ethnicity nor birth weight category differed across quartiles of CVD risk. Weekly frequency of MVPA at Wave I was lower in higher quartiles of predicted CVD risk at Wave IV in both genders, and a similar but weaker association was seen for MVPA at Wave III.

Smoking prevalence at Wave I and Wave III was greater with increasing quartile of predicted CVD risk at Wave IV in both genders. Education level and household income at Wave IV were inversely associated with CVD risk in both genders, and the trends were more pronounced in females, especially for income.

Table 5. Participant characteristics by gender and quartile of predicted 30-year cardiovascular risk

	Females				Males			
	Quartiles of predicted CVD risk				Quartiles of predicted CVD risk			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Count [%, unweighted]	1,960 (43.0)	1,359 (29.8)	764 (16.8)	476 (10.4)	150 (3.9)	751 (19.4)	1,346 (34.7)	1,634 (42.1)
Age, Wave IV mean (SE)	27.4 (0.1)	**28.4 (0.1)**	**28.5 (0.2)**	**29.0 (0.2)**	26.6 (0.2)	**27.3 (0.1)**	**28.2 (0.1)**	**28.8 (0.1)**
Race/Ethnicity [%]								
White	71.8%	71.2%	74.6%	77.5%	72.2%	71.6%	74.5%	75.8%
Black/African-American	14.6%	13.5%	13.3%	13.8%	13.7%	14.4%	11.0%	10.9%
Asian/Pacific Islander	3.0%	3.8%	1.5%	2.3%	4.9%	2.9%	3.7%	2.5%
Hispanic/Latino	10.5%	11.5%	10.6%	6.4%	9.3%	11.1%	10.8%	10.8%
Birth weight category (%)								
Normal	79.9%	81.9%	79.4%	79.0%	75.7%	75.8%	75.3%	74.9%
High	12.1%	8.5%	10.8%	11.0%	22.5%	15.4%	17.5%	17.1%
Low	8.0%	9.6%	9.7%	9.9%	1.8%	8.8%	7.2%	8.1%
Smoker, Wave I [%]	**5.7%**	**9.8%**	**16.6%**	**25.6%**	**0.0%**	**1.1%**	**6.8%**	**16.4%**
Smoker, Wave III [%]	**11.9%**	**22.1%**	**38.2%**	**50.5%**	**13.0%**	**14.2%**	**18.2%**	**41.6%**
Smoker, Wave IV [%]	**4.1%**	**18.9%**	**48.2%**	**66.1%**	**1.9%**	**3.0%**	**14.9%**	**49.3%**
Parent's Highest Education, Wave I [%]								
No college	**43.3%**	**47.4%**	**52.3%**	**59.8%**	**35.4%**	**42.9%**	**43.7%**	**52.1%**
Some college	**18.2%**	**19.0%**	**20.6%**	**22.0%**	**19.0%**	**21.2%**	**20.6%**	**19.1%**
College degree or higher	**38.5%**	**33.6%**	**27.2%**	**18.2%**	**45.6%**	**35.9%**	**35.7%**	**28.8%**
Household income ×$1000, Wave I mean (SE)	51.2 (2.2)	47.8 (2.3)	**38.8 (2.0)**	**40.6 (2.2)**	52.6 (4.6)	47.9 (3.3)	45.8 (1.8)	44.0 (1.7)
MVPA weekly frequency								
Wave I mean (SE)	6.2 (0.1)	**5.6 (0.2)**	**5.2 (0.2)**	**5.1 (0.2)**	8.3 (0.4)	7.6 (0.3)	7.6 (0.2)	**7.0 (0.2)**
Wave III [normalized] mean (SE)	2.6 (0.1)	2.6 (0.1)	**2.0 (0.1)**	2.3 (0.1)	4.0 (0.3)	3.6 (0.2)	**3.3 (0.1)**	**3.0 (0.1)**

Quartiles are defined from pooled sample of both genders. Bold text indicates $p<0.05$; pairwise comparison with Q1 as referent for continuous variables; χ^2 test for any difference for categorical variables. MVPA: moderate-to-vigorous physical activity.

We next describe respondent characteristics across quartiles of the primary exposures, MVPA at Waves I and III. Males and females of younger age and who did not smoke at Wave I had higher MVPA at Wave I (**Table 6**). In females, white race, higher education, and household income were also correlated with greater Wave I MVPA.

Race/ethnicity, parental education, and household income were more consistently related to Wave III MVPA for males and females (**Table 7**). In males, black race and Hispanic ethnicity were associated with greater Wave III MVPA. Smoking and MVPA were most strongly related in concurrent time periods (i.e., measured at the same wave).

Weekly frequency of MVPA at Waves I and III were moderately correlated (Spearman's rank correlation coefficients 0.22 and 0.24 for females and males, respectively). No relationship was seen between birth weight category and MVPA at either wave.

Table 6. Participant characteristics by gender and quartile of Wave I MVPA

	Females				Males			
	Wave I MVPA quartile				Wave I MVPA quartile			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Count [%, unweighted]	1,455 (31.9)	1,197 (26.3)	1,167 (25.6)	740 (16.2)	799 (20.6)	777 (20.0)	1,135 (29.3)	1,170 (30.2)
MVPA weekly frequency								
Wave I mean (SE)	1.7 (0.0)	**4.7 (0.0)**	**7.6 (0.0)**	**12.1 (0.1)**	1.8 (0.1)	**4.7 (0.0)**	**7.8 (0.0)**	**12.4 (0.1)**
Wave III [normalized] mean (SE)	1.9 (0.1)	**2.3 (0.1)**	**2.7 (0.1)**	**3.3 (0.1)**	2.3 (0.2)	2.7 (0.1)	**3.3 (0.1)**	**4.2 (0.1)**
Age, Wave IV mean (SE)	28.6 (0.1)	**28.2 (0.1)**	**27.7 (0.1)**	**27.3 (0.1)**	29.0 (0.1)	**28.5 (0.2)**	**28.0 (0.1)**	**27.8 (0.1)**
Race/Ethnicity [%]								
White	**70.7%**	**68.7%**	**72.9%**	**82.9%**	76.9%	76.2%	72.5%	73.5%
Black/African-American	**17.0%**	**14.7%**	**13.0%**	**8.6%**	10.8%	11.6%	12.2%	11.9%
Asian/Pacific Islander	**1.6%**	**3.9%**	**3.3%**	**3.2%**	2.4%	2.4%	3.5%	3.5%
Hispanic/Latino	**10.7%**	**12.7%**	**10.8%**	**5.3%**	9.9%	9.9%	11.8%	11.1%
Birth weight category (%)								
Normal	78.2%	82.3%	80.6%	80.9%	74.2%	75.6%	76.1%	74.8%
High	11.3%	9.6%	10.8%	11.1%	19.3%	15.3%	16.8%	17.1%
Low	10.6%	8.2%	8.7%	8.0%	6.5%	9.1%	7.1%	8.1%
Smoker, Wave I [%]	**15.4%**	**11.7%**	**8.6%**	**5.5%**	**15.7%**	**12.4%**	**8.2%**	**5.2%**
Smoker, Wave III [%]	24.2%	23.3%	24.4%	23.6%	27.6%	31.0%	26.7%	26.0%
Smoker, Wave IV [%]	22.9%	23.6%	24.9%	20.5%	29.8%	29.4%	25.6%	25.9%
Parent's Highest Education, Wave I [%]								
No college	**54.1%**	**49.1%**	**45.2%**	**38.6%**	51.6%	50.4%	45.1%	43.4%
Some college	**18.9%**	**18.8%**	**21.1%**	**18.3%**	20.2%	18.7%	23.0%	17.7%
College degree or higher	**27.0%**	**32.2%**	**33.7%**	**43.1%**	28.3%	30.9%	31.9%	38.8%
Household income ×$1000, Wave I mean (SE)	44.0 (1.9)	44.9 (2.0)	46.2 (1.8)	**56.1 (3.2)**	45.7 (2.6)	43.1 (2.1)	46.0 (1.9)	47.0 (1.9)

Quartiles are defined from pooled sample of both genders. Boldface indicates $p<0.05$; pairwise comparison with Q1 as referent for continuous variables; χ^2 test for any difference for categorical variables. MVPA: moderate-to-vigorous physical activity

Table 7. Participant characteristics by gender and quartile of Wave III MVPA

	Females				Males			
	Wave III MVPA quartile				Wave III MVPA quartile			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Count [%, unweighted]	1,781 (39.1)	1,068 (23.4)	994 (21.8)	716 (15.7)	1,099 (28.3)	867 (22.3)	933 (24.0)	982 (25.3)
MVPA weekly frequency								
Wave I mean (SE)	5.1 (0.1)	5.5 (0.2)	**6.2 (0.2)**	**7.1 (0.3)**	6.1 (0.2)	**7.1 (0.2)**	**7.7 (0.2)**	**8.9 (0.2)**
Wave III [normalized] mean (SE)	0.4 (0.0)	**2.0 (0.0)**	**3.6 (0.0)**	**6.8 (0.1)**	0.4 (0.0)	**2.0 (0.0)**	**3.7 (0.0)**	**7.3 (0.1)**
Age, Wave IV mean (SE)	28.2 (0.1)	28.1 (0.1)	28.0 (0.2)	28.0 (0.2)	28.3 (0.1)	28.3 (0.2)	28.1 (0.2)	**28.1 (0.1)**
Race/Ethnicity [%]								
White	**69.2%**	**74.4%**	**74.0%**	**78.2%**	**78.9%**	**74.5%**	**73.1%**	**70.2%**
Black/African-American	**17.6%**	**12.3%**	**12.4%**	**9.1%**	**10.8%**	**11.8%**	**10.7%**	**13.8%**
Asian/Pacific Islander	**2.9%**	**2.7%**	**2.4%**	**3.9%**	**2.1%**	**2.8%**	**4.8%**	**2.6%**
Hispanic/Latino	**10.3%**	**10.6%**	**11.3%**	**8.8%**	**8.2%**	**11.0%**	**11.4%**	**13.3%**
Birth weight category (%)								
Normal	81.0%	80.6%	79.7%	79.2%	75.5%	75.5%	74.1%	75.8%
High	10.0%	10.3%	11.3%	12.2%	17.4%	16.9%	18.4%	15.6%
Low	9.1%	9.1%	9.1%	8.7%	7.1%	7.6%	7.5%	8.7%
Smoker, Wave I [%]	12.3%	10.9%	10.8%	8.4%	11.6%	10.5%	7.8%	8.4%
Smoker, Wave III [%]	**28.2%**	**21.0%**	**22.9%**	**18.4%**	**36.5%**	**28.7%**	**23.8%**	**19.0%**
Smoker, Wave IV [%]	**26.4%**	**22.6%**	**21.1%**	**18.7%**	**33.0%**	**27.4%**	**22.8%**	**24.7%**
Parent's Highest Education, Wave I [%]								
No college	**52.5%**	**49.1%**	**45.4%**	**38.1%**	**55.1%**	**42.4%**	**44.0%**	**44.1%**
Some college	**17.2%**	**20.5%**	**20.8%**	**20.9%**	**19.0%**	**21.5%**	**20.1%**	**19.7%**
College degree or higher	**30.3%**	**30.4%**	**33.9%**	**41.0%**	**25.9%**	**36.1%**	**35.9%**	**36.3%**
Household income ×$1000, Wave I mean (SE)	42.6 (1.5)	**48.3 (2.3)**	**48.7 (2.6)**	**53.2 (2.7)**	43.2 (1.9)	45.4 (2.2)	46.0 (2.1)	**48.6 (2.6)**

Quartiles are defined from pooled sample of both genders. Bold text indicates $p<0.05$; pairwise comparison with Q1 as referent for continuous variables; χ^2 test for any difference for categorical variables. MVPA: moderate-to-vigorous physical activity

Regression model results

The fully adjusted model included age, race, smoking at Wave I, smoking at Wave III, educational attainment, and household income at Wave IV. Model coefficients and statistics, including models without birth weight and without MVPA, are reported in **Appendix Table A4** and **Table A5**. In fully adjusted models (Model 3), the coefficients for high birth weight and low birth weight were positive for both genders, representing positive estimated effects of HBW and LBW on predicted 30-year CVD risk at Wave IV (early adulthood), given no physical activity (i.e., when $MVPA_1=0$ and $MVPA_3=0$). The coefficients for $MVPA_1$ and $MVPA_3$ were close to zero, representing small estimated effects of $MVPA_1$ and $MVPA_3$ on predicted CVD risk among those born at normal birth weight. This suggests that frequency of physical activity in adolescence and young adulthood does not have an appreciable independent association with the adulthood cardiovascular risk factors that make up the risk prediction algorithm.

Associations between MVPA frequency at Wave I (adolescence) and predicted 30-year CVD risk at Wave IV (early adulthood) were significantly stronger in HBW than NBW in females (interaction $p=0.015$) and males (interaction $p=0.094$). Interactions between HBW and MVPA at Wave III were not significant (interaction $p>0.1$). LBW did not modify the associations between MVPA at Waves I or III and CVD risk (interaction $p>0.1$).

In both genders, coefficients for Wave IV age, Wave I smoking, and Wave III smoking were positive, indicating positive estimated effects on predicted CVD risk independent of other variables. Non-white race/ethnicity and higher educational attainment generally had negative coefficients, suggesting independent negative estimated effects on predicted CVD risk.

Physical activity–CVD risk relationships by birth weight category are depicted graphically in **Figure 4–7**. In females born with high birth weight, greater MVPA frequency at Wave I (adolescence) was associated with lower predicted 30-year CVD risk at Wave IV (early adulthood) (**Figure 4**). For example, a HBW girl at the 10^{th} percentile for MVPA frequency at Wave I (1.5 MVPA bouts per week) has a predicted 30-year CVD risk at Wave IV that is 0.9 percentage points greater (5.6% vs 4.7%, 19% increased risk) than a HBW girl at the 90^{th} percentile of Wave I MVPA (12.5 MVPA bouts per week), assuming mean values for all other dependent variables. In females born with low or normal birth weight, MVPA frequency at Wave I (adolescence) displayed a weak, non-significant relationship with predicted 30-year CVD risk at Wave IV (early adulthood). MVPA frequency at Wave III in females of any birth weight was not significantly associated with Wave IV predicted CVD risk (**Figure 5**).

In males of any birth weight, MVPA frequency at Wave I (adolescence) and Wave III (early adulthood) was not significantly associated with predicted 30-year CVD risk at Wave IV (early adulthood) (**Figure 6**). For the association of Wave I MVPA with CVD risk, the strongest relationship was an inverse association in HBW males. For the association of Wave III MVPA with CVD risk, the strongest relationship was an inverse association in LBW males (**Figure 7**).

Normal birth weight:
β_t = 0.0010
(-0.0048, 0.0069)

High birth weight:
β_t = -0.0183
(-0.0317, -0.0049)

Low birth weight:
β_t = 0.0026
(-0.0155, 0.0207)

β_t = coefficient of natural log-transformed CVD 30-year risk (model used in regression).

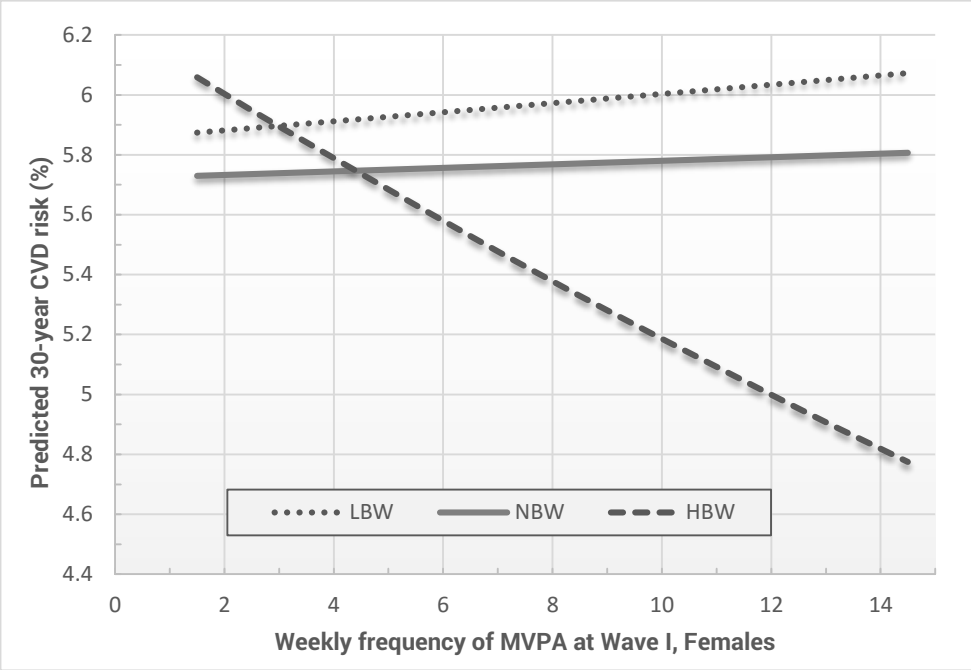

Figure 4. Estimated effect of Wave I MVPA on predicted 30-year CVD risk in females

Normal birth weight:
β_t = 0.0008
(-0.0090, 0.0106)

High birth weight:
β_t = -0.0007
(-0.0223, 0.0210)

Low birth weight:
β_t = -0.0013
(-0.0233, 0.0207)

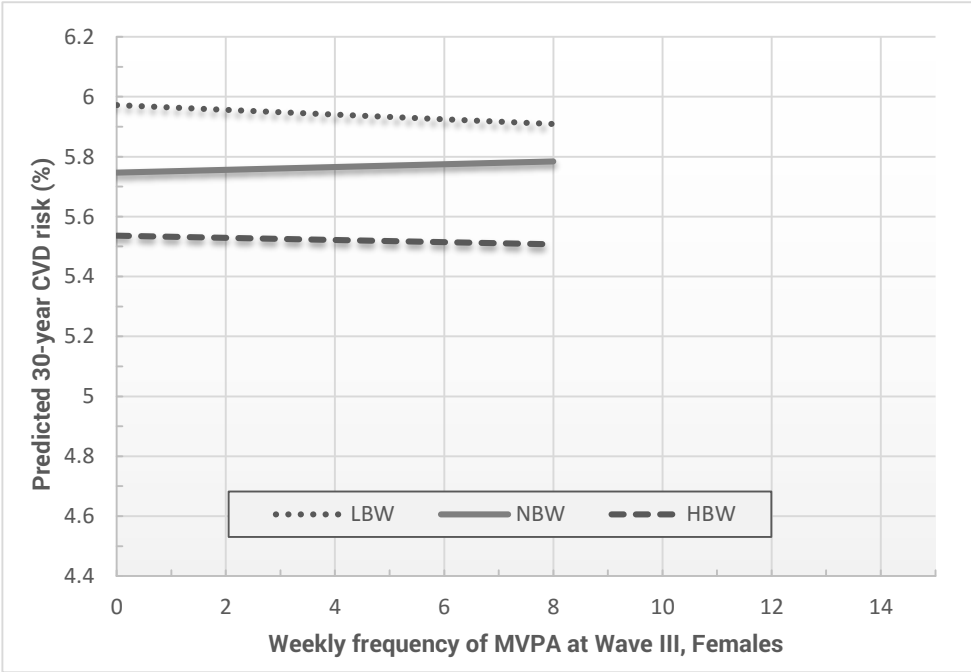

Figure 5. Estimated effect of Wave III MVPA on predicted 30-year CVD risk in females

Normal birth weight:
β_t = 0.0030
(-0.0024, 0.0084)

High birth weight:
β_t = -0.0076
(-0.0186, 0.0033)

Low birth weight:
β_t = -0.0048
(-0.0192, 0.0097)

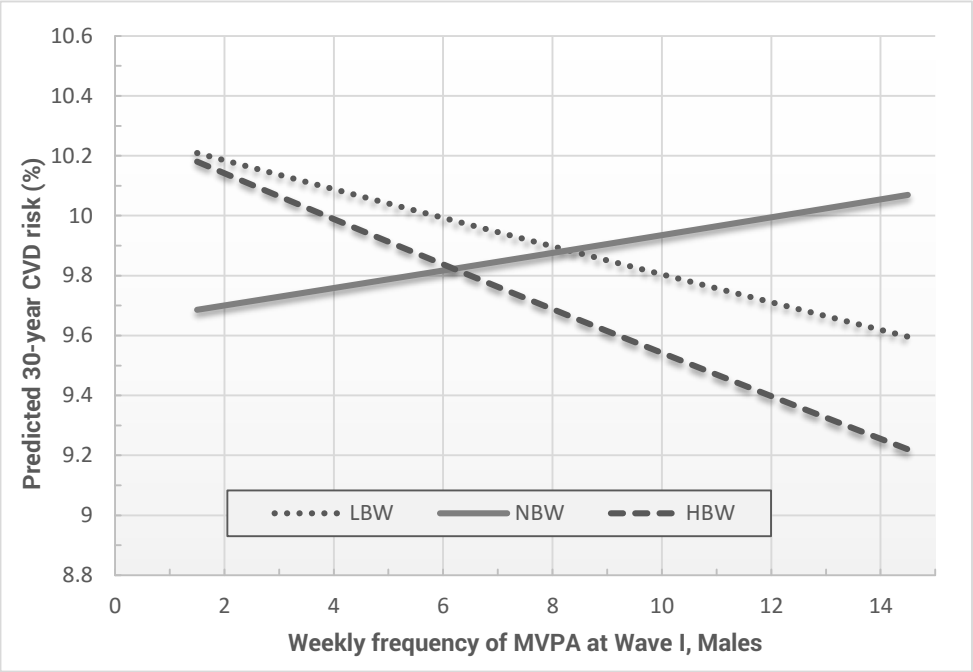

Figure 6. Estimated effect of Wave I MVPA on predicted 30-year CVD risk in males

Normal birth weight:
β_t = -0.0051
(-0.0126, 0.0024)

High birth weight:
β_t = -0.0022
(-0.0144, 0.0100)

Low birth weight:
β_t = -0.0094
(-0.0375, 0.0187)

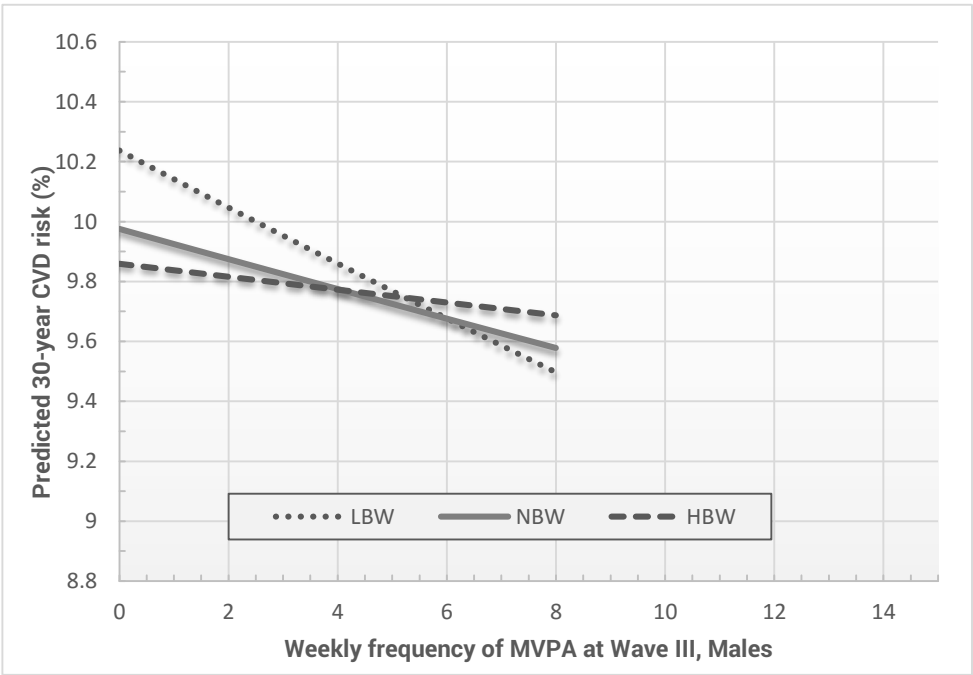

Figure 7. Estimated effect of Wave III MVPA on predicted 30-year CVD risk in males

Discussion

In this large, nationally representative longitudinal adolescent cohort, we found important heterogeneity across birth weight and gender in the associations between frequency of moderate-to-vigorous intensity physical activity and predicted 30-year cardiovascular risk. Central to our hypothesis was the question of effect modification, or interaction. We observed a significant interaction between birth weight and physical activity in adolescence for females and males. In particular, adolescent physical activity was more strongly associated with predicted CVD risk in those who had high birth weight; greater physical activity was associated with lower predicted CVD risk in this subgroup. Our finding that adolescent physical activity but not adult physical activity is inversely related to predicted CVD risk in those born at high birth weight suggests that adolescence may be a sensitive window for the "second hit" of physical inactivity on the pathway to cardiovascular disease in people exposed to prenatal overnutrition *in utero* (the "first hit").

That we found no significant association between physical activity assessed in young adulthood and predicted CVD risk does not mean that adult physical activity is not important in cardiovascular health. There is abundant evidence that physical activity is beneficial to health at all stages of life. However, adolescence is a period of significant weight gain for many people, and it may be that greater activity in adolescence has a particularly strong influence in preventing obesity and other cardiovascular risk factors, with effects that persist into adulthood. Another contributing factor may be that the lower and smaller range of physical activity frequency reported among participants in Wave III compared to Wave I effectively reduced statistical power and therefore the ability to detect a significant association at Wave III.

The few previous studies on birth weight–physical activity interaction and health outcomes have primarily focused on type 2 diabetes, metabolic syndrome, and obesity.[39–44] These studies indicate that physical activity may mitigate effects of low and high birth weight on metabolic outcomes, and our results indicate that physical activity may also mitigate effects of high birth weight on cardiovascular outcomes. Because many risk factors are common to diabetes, obesity, and CVD, our findings make sense within the emerging understanding of developmental programming effects on adult chronic disease, and suggest potential avenues to reduce disease risk.

With regard to gender, we found a stronger association between Wave I MVPA frequency and predicted 30-year CVD risk in high birth weight females compared to high birth weight males. This is supported by gender-specific effects in developmental programming of cardiovascular disease reported in the literature.[43,66–68] An additional consideration is that mean birth weight for males tends to be slightly higher than for females[72], but we used

the same threshold for high birth weight, 4 kg (8 lb, 13 oz), in both genders, as others have.[73–75] Thus, the females in the high birth weight category tended to be farther above the mean for their gender than the males in the same category (1.04 kg greater versus 0.974 kg greater). Being more extreme in distribution, the female HBW group may represent a greater influence of adverse developmental programming, though any such influence would likely be minor.

We also noted non-significant associations between birth weight and predicted CVD risk that were stronger in females (Model 2, **Appendix Table A4** and **Table A5**) and stronger for low birth weight than high birth weight. This gender difference is generally consistent with findings from literature. For instance, in a Scottish cohort of more than 10,000 people followed prospectively from birth, a stronger inverse association between birth weight and coronary heart disease and stroke was seen in women.[76] A similar female-specific effect has also been observed with respect to the interaction of birth weight and physical activity on serum leptin, a marker of adiposity.[41] A study of more than 190,000 individuals from 20 Scandinavian cohorts indicated an inverse association between birth weight and systolic blood pressure in men, but a J-shaped curve in women, with SBP decreasing with increasing birth weight below 4 kg but increasing with birth weight above 4 kg.[66]However, in a western European cohort of healthy young adults, low birth weight was associated with an increased 10-year Framingham risk score for coronary artery disease in young adulthood, with a greater effect seen in men than women.[10]

As seen in **Table 3**, the proportion of low birth weight females who developed diabetes by Wave IV was approximately double that of normal and high birth weight females (10.8% versus 5.9% and 5.4%, respectively), and this appeared to underlie the significantly elevated mean predicted 30-year CVD risk in the LBW female group (7.5% versus 6.8% and 6.8%). No such discrepancy was seen in LBW males, and it is noteworthy that HBW individuals of both genders had a slightly lower proportion of diabetes at Wave IV than NBW individuals, despite being more likely to have a diabetic mother (risk ratio 1.73 [95% CI, 1.36–2.21]) or obese mother (RR 1.53 [1.33–1.76]). This indicates that LBW and not HBW (and by extension prenatal undernutrition but not prenatal overnutrition) was associated with higher predicted CVD risk overall.

Public health implications

This research quantifies the importance of prenatal overnutrition, as approximated by high birth weight, as a factor that increases susceptibility to the effects of physical inactivity on cardiovascular health in adolescence and young adulthood. Because the burden of diabetes and cardiovascular disease is expected to expand worldwide over the coming decades, understanding

the interaction between these risk factors has significant implications for public health prevention strategies. The results of this study suggest that identification of prenatal overnutrition and elevated cardiovascular risk in young populations would allow tailored interventions to prevent and mitigate modifiable risk factors at an early stage. Our findings may aid clinicians and policy-makers alike in deploying novel individual- and population-level interventions to mitigate morbidity and mortality from cardiovascular disease in those with adverse early life exposures.

Our primary research question involved promising but little-studied interactions between behavioral factors, which are modifiable at the individual level, and developmental factors, which are modifiable for future generations. Thus, the public health implications are twofold, with both immediate and long-term potential to mitigate and prevent cardiovascular disease. Lastly, these findings may help shift focus from a deterministic view of developmentally programmed disease toward actionable steps forward in the fight against cardiovascular disease and diabetes.

Strengths and limitations

This study has several strengths. The data for analysis were drawn from a very large, validated prospective cohort study with 14 years of follow-up; therefore, this study has both a greater sample size and a longer measurement period than previous research on this subject. Indeed, no studies have sought to determine interactions of physical activity with prenatal factors and their associations with the multiple outcomes that constitute overall cardiovascular risk. Second, our use of repeated measures of physical activity provided greater resolution in exposure assessment and demonstrated differential effects of physical activity at different stages of life. Third, our outcome was based on objective clinical measures that are established components of cardiometabolic risk, using data from Add Health that have only recently become available.

Our findings are subject to several limitations. First, although the data were collected in a longitudinal survey, the outcome variable was measured at a point in time (Wave IV) rather than over a period of follow-up. However, temporality is clear given that exposure variables were measured before the component variables of the outcome variable. Second, 4148 participants (33%) were excluded due to missing data, which may have introduced selection bias, although as noted above, the differences in characteristics between those included and those excluded were relatively minor and did not include differences in the major exposures of interest (MVPA at Wave I or III, or birth weight category). Third, the exposure measures and control variables were self-reported and thus subject to measurement bias from under- or overreporting, but our measures for these variables are similar to those in other studies. For instance, the weighted smoking prevalence at Wave IV of 23.5%

for women and 27.1% for men is close to that expected based on 2007 NHANES findings for adults age 25-44 (19.6% and 26.0%, respectively).[77] Also, between high school and early adulthood, self-reported MVPA in this cohort declined significantly, which is consistent with data from other cohorts.[78,79] Our scaling of the young adulthood frequency values to account for questionnaire changes follows methods used previously in the Add Health cohort[63]; although this adjustment may have altered the magnitude of associations, it is unlikely to have altered their direction or significance.

Fourth, high birth weight is an imperfect surrogate measure of prenatal overnutrition, in part because of the heterogeneity within a group defined solely by weight at birth, as noted above; size for gestational age would be better but was not available in the Add Health study. The addition of maternal measures of obesity and diabetes would increase specificity as well, but Add Health's parental interview only asked whether the mother was obese or diabetic at Wave I, which was at least 12 years after the participants were *in utero*. Fifth, the algorithm used in our outcome measure has not been validated in an external population to our knowledge. Although it was internally validated by Pencina et al. and is an extension of earlier algorithms based on the Framingham cohort that have been extensively tested in various cohorts, some caution is nonetheless needed in generalizing our results.

Sixth, exact values of lipids were not reported in Add Health due to stated limitations in reliability and precision of the measurements, which used dried capillary whole blood and two assay methods; we converted the lipid deciles into absolute values derived from NHANES 2007-08 and 2009-10 to allow use of the risk prediction algorithm. Given the nationally representative sample in Add Health, it is unlikely that NHANES deciles differ significantly, and differential misclassification that would inflate effect sizes is very unlikely. Seventh, the estimated effect sizes we found were modest, but this is not unexpected given the highly multifactorial nature of cardiovascular disease and the young age of this population. Finally, the relatively small numbers of low and high birth weight participants limited statistical power to detect MVPA–CVD risk associations and MVPA–birth weight interactions within birth weight groups. However, we still had a large overall sample and we did observe significant interactions.

We note that the associations and interactions we found are between physical activity, birth weight, and a panel of CVD risk factors rather than actual cardiovascular events such as myocardial infarction and stroke. Thus, the effect of physical activity that we have inferred from our results is an estimated effect upon the behavioral and modifiable components that contribute to CVD risk (i.e., smoking, diabetes, blood lipids, and blood pressure); it is not an estimated effect derived from observed CVD events, which were not assessed in Add Health. However, two of the largest contributors to CVD risk are age

and sex, which are not modifiable in the same sense and cannot be acted upon by physical activity in a causal pathway, although our results confirmed that they are indeed correlated with physical activity level. Future research could answer this question in a long-term study that assessed birth weight, adolescent physical activity, and incident cardiovascular events over long-term follow-up into middle age or beyond.

Conclusions

In our overall analysis, physical activity in adolescence was not significantly associated with predicted 30-year cardiovascular risk in early adulthood, but this relationship was modified by birth weight and gender. Specifically, greater adolescent physical activity was associated with lower long-term CVD risk in those who had high birth weight, especially HBW females. These data, in the context of recent literature in developmental programming, indicate that adolescent physical inactivity may be a "second hit" in those who experienced prenatal overnutrition. Importantly, children born at high birth weight may be especially sensitive to the effects of physical activity on reducing risk of cardiovascular disease later in life, with important implications for health policy.

References

1. World Health Organization. Cardiovascular diseases (CVDs). *Fact sheet N°317*. 2015. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed June 25, 2015.

2. Barker D. The fetal and infant origins of disease. *Eur J Clin Invest*. 1995. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2362.1995.tb01730.x/full. Accessed November 17, 2014.

3. Dyer JS, Rosenfeld CR. Metabolic imprinting by prenatal, perinatal, and postnatal overnutrition: a review. *Semin Reprod Med*. 2011;29(3):266–76. doi:10.1055/s-0031-1275521.

4. Heard E, Martienssen RA. Transgenerational epigenetic inheritance: myths and mechanisms. *Cell*. 2014;157(1):95–109. doi:10.1016/j.cell.2014.02.045.

5. Drake a. J, Walker BR. The intergenerational effects of fetal programming: Non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol*. 2004;180(1):1–16. doi:10.1677/joe.0.1800001.

6. Blackmore HL, Ozanne SE. Programming of cardiovascular disease across the life-course. *J Mol Cell Cardiol*. 2014;83:122–130. doi:10.1016/j.yjmcc.2014.12.006.

7. Barker DJ, Clark PM. Fetal undernutrition and disease in later life. *Rev Reprod*. 1997;2(2):105–112. doi:10.1530/ror.0.0020105.

8. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr*. 2007;4(2b). doi:10.1079/PHN2001145.

9. Mu M, Wang SF, Sheng J, et al. Birth weight and subsequent blood pressure: A meta-analysis. *Arch Cardiovasc Dis*. 2012;105(2):99–113. doi:10.1016/j.acvd.2011.10.006.

10. Vos LE, Oren A, Bots ML, Gorissen WHM, Grobbee DE, Uiterwaal CSPM. Birth size and coronary heart disease risk score in young adulthood. The atherosclerosis risk in young adults (ARYA) study. *Eur J Epidemiol*. 2006;21(1):33–38. doi:10.1007/s10654-005-4658-8.

11. Huxley R, Owen CG, Whincup PH, et al. Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr*. 2007;85(5):1244–1250.

12. Whincup P, Kaye S, Owen C, et al. Birth weight and risk of type 2 diabetes: a systematic review. 2008;300(24). Available at: http://discovery.ucl.ac.uk/90839/.

13. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol*. 2007;165(8):849–57. doi:10.1093/aje/kwk071.

14. Pfab T, Slowinski T, Godes M, Halle H, Priem F, Hocher B. Low birth weight, a risk factor for cardiovascular diseases in later life, is already associated with elevated fetal glycosylated hemoglobin at birth. *Circulation*. 2006;114(16):1687–1692. doi:10.1161/CIRCULATIONAHA.106.625848.

15. Lawlor D a, Smith GD, O'Callaghan M, et al. Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *Am J Epidemiol*. 2007;165(4):418–24. doi:10.1093/aje/kwk030.

16. Schellong K, Schulz S, Harder T, Plagemann A. Birth Weight and Long-Term Overweight Risk: Systematic Review and a Meta-Analysis Including 643,902 Persons from 66 Studies and 26 Countries Globally. *PLoS One*. 2012;7(10). doi:10.1371/journal.pone.0047776.

17. Skilton MR, Siitonen N, Würtz P, et al. High birth weight is associated with obesity and increased carotid wall thickness in young adults: The cardiovascular risk in young finns study. *Arterioscler Thromb Vasc Biol*. 2014;34(5):1064–1068. doi:10.1161/ATVBAHA.113.302934.

18. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatric Obesity*. 2014.

19. Wei J-N, Sung F-C, Li C-Y, et al. Low Birth Weight and High Birth Weight Infants Are Both at an Increased Risk to Have Type 2 Diabetes Among Schoolchildren in Taiwan. *Diabetes Care*. 2003;26(2):343–348. doi:10.2337/diacare.26.2.343.

20. Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ*. 1997;315(7105):396–400. doi:10.1136/bmj.315.7105.396.

21. Ryan H, Trosclair A, Gfroerer J. Adult current smoking: Differences in definitions and prevalence estimates - NHIS and NSDUH, 2008. *J Environ Public Health*. 2012;2012. doi:10.1155/2012/918368.

22. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation*. 1996;94(12):3246–3250. doi:10.1161/01.CIR.94.12.3246.

23. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. *Circulation*. 1996;94(6):1310–1315. doi:10.1161/01.CIR.94.6.1310.

24. Lurbe E, Garcia-Vicent C, Torro MI, Aguilar F, Redon J. Associations of birth weight and postnatal weight gain with cardiometabolic risk parameters at 5 years of age. *Hypertension*. 2014;63(6):1326–1332. doi:10.1161/HYPERTENSIONAHA.114.03137.

25. Filler G, Yasin A, Kesarwani P, Garg AX, Lindsay R, Sharma AP. Big Mother or Small Baby: Which Predicts Hypertension? *J Clin Hypertens*. 2011;13(1):35–41. doi:10.1111/j.1751-7176.2010.00366.x.

26. Conen D, Tedrow UB, Cook NR, Buring JE, Albert CM. Birth Weight Is a Significant Risk Factor for Incident Atrial Fibrillation. *Circulation*. 2010;122(8):764–770. doi:10.1161/CIRCULATIONAHA.110.947978.

27. Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Incidence of atrial fibrillation in relation to birth weight and preterm birth. *Int J Cardiol*. 2015;178:149–152. doi:10.1016/j.ijcard.2014.10.138.

28. Zhang Y, Li H, Liu S-J, et al. The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertens Res*. 2013;(1):1–11. doi:10.1038/hr.2013.33.

29. Stuart A, Amer-Wåhlin I, Persson J, Källen K. Long-term cardiovascular risk in relation to birth weight and exposure to maternal diabetes mellitus. *Int J Cardiol*. 2013;168(3):2653–2657. doi:10.1016/j.ijcard.2013.03.032.

30. Lawani SO, Demerath EW, Lopez FL, et al. Birth weight and the risk of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk In Communities (ARIC) study. *BMC Cardiovasc Disord*. 2014;14(1):69. doi:10.1186/1471-2261-14-69.

31. Myers J, McAuley P, Lavie CJ, Despres J-P, Arena R, Kokkinos P. Physical Activity and Cardiorespiratory Fitness as Major Markers of Cardiovascular Risk: Their Independent and Interwoven Importance to Health Status. *Prog Cardiovasc Dis*. 2015;57(4):306–314. doi:10.1016/j.pcad.2014.09.011.

32. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care*. 2007;30(3):744–52. doi:10.2337/dc06-1842.

33. Ekelund U, Sardinha L. Associations between objectively assessed physical activity and indicators of body fatness in 9-to 10-y-old European children: a population-based study from 4 distinct. *Am J Clin Nutr*. 2004;(6):1–3. Available at: http://ajcn.nutrition.org/content/80/3/584.short. Accessed November 18, 2014.

34. Steele RM, Brage S, Corder K, Wareham NJ, Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol*. 2008;105(1):342–51. doi:10.1152/japplphysiol.00072.2008.

35. Gordon-Larsen P, Adair LS, Nelson MC, Popkin BM. Five-year obesity incidence in the transition period between adolescence and adulthood: the National Longitudinal Study of Adolescent Health. *Am J Clin Nutr*. 2004;80(3):569–575. doi:80/3/569 [pii].

36. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008;117:743–753. doi:10.1161/CIRCULATIONAHA.107.699579.

37. Rajia S, Chen H, Morris MJ. Voluntary post weaning exercise restores metabolic homeostasis in offspring of obese rats. *Nutr Metab Cardiovasc Dis*. 2013;23(6):574–81. doi:10.1016/j.numecd.2011.12.009.

38. Bahari H, Caruso V, Morris MJ. Late-onset exercise in female rat offspring ameliorates the detrimental metabolic impact of maternal obesity. *Endocrinology*. 2013;154(10):3610–21. doi:10.1210/en.2013-1059.

39. Laaksonen D, Lakka H, Lynch J. Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. *Diabetes Care*. 2003. Available at: http://care.diabetesjournals.org/content/26/7/2156.short. Accessed November 3, 2014.

40. Eriksson JG, Ylihärsilä H, Forsén T, Osmond C, Barker DJP. Exercise protects against glucose intolerance in individuals with a small body size at birth. *Prev Med (Baltim)*. 2004;39(1):164–7. doi:10.1016/j.ypmed.2004.01.035.

41. Labayen I, Ortega FB, Moreno L a, et al. Physical activity attenuates the negative effect of low birth weight on leptin levels in European adolescents; the HELENA study. *Nutr Metab Cardiovasc Dis*. 2013;23(4):344–9. doi:10.1016/j.numecd.2011.12.004.

42. Ortega FB, Ruiz JR, Hurtig-Wennlöf A, et al. Physical activity attenuates the effect of low birth weight on insulin resistance in adolescents: findings from two observational studies. *Diabetes*. 2011;60(9):2295–9. doi:10.2337/db10-1670.

43. Boone-Heinonen J, Markwardt S, Fortmann SP, Thornburg KL. Overcoming birth weight: can physical activity mitigate birth weight-related differences in adiposity? *Pediatr Obes*. 2015:n/a–n/a. doi:10.1111/ijpo.12040.

44. Ridgway CL, Brage S, Anderssen S a, Sardinha LB, Andersen LB, Ekelund U. Do physical activity and aerobic fitness moderate the association between birth weight

and metabolic risk in youth?: the European Youth Heart Study. *Diabetes Care*. 2011;34(1):187–92. doi:10.2337/dc10-1178.

45. Harris KM, Halpern CT, Whitsel E, et al. The National Longitudinal Study of Adolescent to Adult Health: Research Design. 2009. Available at: http://www.cpc.unc.edu/projects/addhealth/design. Accessed June 25, 2015.

46. Add Health. Available at: http://www.cpc.unc.edu/projects /addhealth/design.

47. Andridge RR, Little RJA. A Review of Hot Deck Imputation for Survey Non-response. *Int Stat Rev*. 2010;78(1):40–64. doi:10.1111/j.1751-5823.2010.00103.x.

48. Mander A, Clayton D. Hotdeck: Stata module to perform hot deck imputation. 2007.

49. Whitsel EA, Cuthbertson CC, Tabor JW, et al. *Add Health Wave IV Documentation: Lipids*.; 2013.

50. Whitsel EA, Tabor JW, Nguyen QC, et al. *Add Health Wave IV Documentation: Measures of Glucose Homeostasis*.; 2012.

51. Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: The framingham heart study. *Circulation*. 2009;119(Cvd):3078–3084. doi:10.1161/CIRCULATIONAHA.108.816694.

52. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol*. 1979;110:281–290.

53. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA, National Lipid Association Taskforce on Non HDLC. The importance of non-HDL cholesterol reporting in lipid management. *J Clin Lipidol*. 2008;2(4):267–273. doi:10.1016/j.jacl.2008.06.013.

54. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):337–45. doi:10.1161/CIRCOUTCOMES.110.959247.

55. Arsenault BJ, Rana JS, Stroes ESG, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healt. *J Am Coll Cardiol*. 2009;55(1):35–41. doi:10.1016/j.jacc.2009.07.057.

56. NHANES 2007-2008. Available at: http://wwwn.cdc.gov/nchs/nhanes/search/nhanes07_08.aspx.

57. NHANES 2009-2010. Available at: http://wwwn.cdc.gov/Nchs/Nhanes/Search/nhanes09_10.aspx.

58. Rosengren A, Wilhelmsen L, Wedel H. Coronary heart disease, cancer and mortality in male middle-aged light smokers. *J Intern Med*. 1992;231(4):357–362.

59. Prescott E, Scharling H, Osler M, Schnohr P. Importance of light smoking and inhalation habits on risk of myocardial infarction and all cause mortality. A 22 year follow up of 12 149 men and women in The Copenhagen City Heart Study. *J Epidemiol Community Health*. 2002;56(9):702–706. doi:10.1136/jech.56.9.702.

60. Law MR, Wald NJ. Environmental tobacco smoke and ischemic heart disease. *Prog Cardiovasc Dis*. 2003;46(1):31–38.

61. Bjartveit K, Tverdal a. Health consequences of smoking 1-4 cigarettes per day. *Tob Control*. 2005;14(5):315–320. doi:10.1136/tc.2005.011932.

62. Sallis JF, McKenzie TL, Kolody B, Lewis M, Marshall S, Rosengard P. *Effects of health-related physical education on academic achievement: project SPARK.*; 1999. doi:10.1080/02701367.1999.10608030.

63. Richardson AS, North KE, Graff M, et al. Moderate to vigorous physical activity interactions with genetic variants and body mass index in a large US ethnically diverse cohort. *Pediatr Obes*. 2014;9(2):e35–e46. doi:10.1111/j.2047-6310.2013.00152.x.

64. Gordon-Larsen P, Nelson MC, Popkin BM. Longitudinal physical activity and sedentary behavior trends: Adolescence to adulthood. *Am J Prev Med*. 2004;27(4):277–283. doi:10.1016/j.amepre.2004.07.006.

65. Add Health. Questionnaire Codebooks for Waves I, II, III and IV. Available at: http://www.cpc.unc.edu/projects/addhealth/codebooks.

66. Gamborg M, Byberg L, Rasmussen F, et al. Birth weight and systolic blood pressure in adolescence and adulthood: Meta-regression analysis of sex- and age-specific results from 20 nordic studies. *Am J Epidemiol*. 2007;166(6):634–645. doi:10.1093/aje/kwm042.

67. Moritz KM, Cuffe JSM, Wilson LB, et al. Review: Sex specific programming: A critical role for the renal renin–angiotensin system. *Placenta*. 2010;31:S40–S46. doi:10.1016/j.placenta.2010.01.006.

68. Intapad S, Ojeda NB, Dasinger JH, Alexander BT. Sex Differences in the Developmental Origins of Cardiovascular Disease. *Physiology*. 2014;29(2):122–132. doi:10.1152/physiol.00045.2013.

69. Luoto R, Uutela a, Puska P. Occasional smoking increases total and cardiovascular mortality among men. *Nicotine Tob Res*. 2000;2(2):133–139.

70. Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis*. 2007;17(1):143–152.

71. Chen P, Chantala K. *Guidelines for analyzing Add Health data*.; 2014.

72. WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development*. Geneva; 2006.

73. Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the United States: Determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol*. 2003;188(5):1372–1378. doi:10.1067/mob.2003.302.

74. Martin J a, Hamilton BE, Ventura SJ, et al. Births: final data for 2009. *Natl Vital Stat Rep*. 2011;60(1):1–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22670489.

75. Committee on Scientific Evaluation of WIC Nutrition Risk Criteria - Institute of Medicine. *WIC Nutrition Risk Criteria : A Scientific Assessment*. National Academies Press; 1996.

76. Lawlor D a., Ronalds G, Clark H, Smith GD, Leon D a. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: Findings from the Aberdeen children of the 1950s prospective cohort study. *Circulation*. 2005;112(10):1414–1418. doi:10.1161/CIRCULATIONAHA.104.528356.

77. CDC. Cigarette Smoking Among Adults — United States, 2007. *Morb Mortal Wkly Rep*. 57(45):1221–1226.

78. Taverno Ross SE, Larson N, Graham DJ, Neumark-Sztainer D. Longitudinal Changes in Physical Activity and Sedentary Behavior From Adolescence to Adulthood: Comparing U.S.–Born and Foreign-Born Populations. *J Phys Act Heal*. 2014;11(3):519–527. doi:10.1123/jpah.2011-0359.

79. Kwon S, Janz KF, Letuchy EM, Burns TL, Levy SM. Developmental Trajectories of Physical Activity, Sports, and Television Viewing During Childhood to Young Adulthood. *JAMA Pediatr*. 2015;169(7):666–672. doi:10.1001/jamapediatrics.2015.0327.

Appendices

Table A1. Median cholesterol values for deciles derived from NHANES 2007–10 data

Decile	Total cholesterol (mg/dL)		Decile	HDL cholesterol (mg/dL)
1	126		1	31
2	144		2	37
3	156		3	42
4	167		4	45
5	176		5	49
6	187		6	52
7	198		7	56
8	212		8	61
9	230		9	67
10	262		10	80

Table A2. Therapeutic classifications for prescription anti-hypertensive medications

Code	Therapeutic classification
041	agents for hypertensive emergencies
042	angiotensin converting enzyme inhibitors
043	antiadrenergic agents, peripherally acting
044	antiadrenergic agents, centrally acting
047	beta-adrenergic blocking agents
048	calcium channel blocking agents
049	diuretics
052	peripheral vasodilators
053	vasodilators
055	antihypertensive combinations
056	angiotensin II inhibitors
154	loop diuretics
155	potassium-sparing diuretics
156	thiazide diuretics
274	cardioselective beta blockers
275	non-cardioselective beta blockers
340	aldosterone receptor antagonists
342	renin inhibitors

Table A3. Add Health survey questions from which MVPA variables are derived

Wave	Question	Answer choices
Wave I	During the past week, how many times did you go rollerblading, roller-skating, skate-boarding, or bicycling?	• Not at all • 1 or 2 times • 3 or 4 times • 5 or more times • Don't know
	During the past week, how many times did you play an active sport, such as baseball, softball, basketball, soccer, swimming, or football?	
	During the past week, how many times did you do exercise, such as jogging, walking, karate, jumping rope, gymnastics or dancing?	
Wave III	In the past seven days, how many times did you bicycle, skateboard, dance, hike, hunt, or do yard work?	• Not at all • 1 time • 2 times • 3 times • 4 times • 5 times • 6 times • 7 or more times • Don't know
	In the past seven days, how many times did you roller blade, roller skate, downhill ski, snow board, play racquet sports, or do aerobics?	
	In the past seven days, how many times did you participate in strenuous team sports such as football, soccer, basketball, lacrosse, rugby, field hockey, or ice hockey?	
	In the past seven days, how many times did you participate in individual sports such as running, wrestling, swimming, cross-country skiing, cycle racing, or martial arts?	
	In the past seven days, how many times did you participate in gymnastics, weight lifting, or strength training?	
	In the past seven days, how many times did you walk for exercise?	

Table A4. Coefficients from gender-stratified multivariable linear regression of natural log-transformed predicted 30-year CVD risk: females

	FEMALES					
	Model 1		Model 2		Model 3	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p
High birth weight (HBW)*			-0.025 (-0.074, 0.024)	0.32	0.089 (-0.030, 0.208)	0.14
Low birth weight (LBW)*			0.031 (-0.034, 0.096)	0.34	0.029 (-0.081, 0.138)	0.61
MVPA at Wave I (MVPA1)	-0.001 (-0.006, 0.004)	0.67			0.001 (-0.005, 0.007)	0.73
HBW × MVPA1					-0.019 (-0.035, -0.004)	**0.02**
LBW × MVPA1					0.002 (-0.017, 0.020)	0.87
MVPA at Wave III (MVPA3)	0.000 (-0.009, 0.009)	0.96			0.001 (-0.009, 0.011)	0.87
HBW × MVPA3					-0.001 (-0.025, 0.022)	0.90
LBW × MVPA3					-0.002 (-0.025, 0.021)	0.85
Age at Wave IV	0.095 (0.084, 0.106)	**0.00**	0.096 (0.085, 0.106)	**0.00**	0.096 (0.085, 0.106)	**0.00**
Black race*	0.016 (-0.033, 0.064)	0.52	0.013 (-0.035, 0.060)	0.60	0.013 (-0.036, 0.061)	0.61
Asian race*	-0.044 (-0.152, 0.063)	0.42	-0.048 (-0.158, 0.062)	0.39	-0.049 (-0.160, 0.062)	0.38
Hispanic ethnicity*	-0.040 (-0.110, 0.031)	0.27	-0.039 (-0.108, 0.031)	0.27	-0.040 (-0.109, 0.030)	0.26
Smoking at Wave I	0.043 (-0.030, 0.117)	0.25	0.044 (-0.030, 0.119)	0.24	0.042 (-0.031, 0.114)	0.26
Smoking at Wave III	0.325 (0.274, 0.377)	**0.00**	0.325 (0.273, 0.377)	**0.00**	0.325 (0.273, 0.377)	**0.00**
Parent some college at W1*	-0.012 (-0.063, 0.038)	0.63	-0.011 (-0.061, 0.038)	0.64	-0.011 (-0.061, 0.039)	0.67
Parent college degree at W1*	-0.112 (-0.159, -0.064)	**0.00**	-0.110 (-0.156, -0.064)	**0.00**	-0.109 (-0.156, -0.062)	**0.00**
Household income at Wave I	-0.001 (-0.001, 0.000)	**0.00**	-0.001 (-0.001, 0.000)	**0.00**	-0.001 (-0.001, 0.000)	**0.00**
Constant	-0.883 (-1.191, -0.575)	**0.00**	-0.907 (-1.203, -0.611)	**0.00**	-0.909 (-1.215, -0.603)	**0.00**

Model 1: excludes BW variables and interaction terms. Model 2: excludes MVPA variables and interaction terms. Model 3: fully adjusted model with BW indicator variables, MVPA variables, BW×MVPA interaction terms, age at Wave IV, race/ethnicity, smoking at Wave I, smoking at Wave III, educational attainment, and household income at Wave IV. Analytic sample *n*=4559 females. * indicator variable. MVPA: moderate-to-vigorous physical activity.

Table A5. Coefficients from gender-stratified multivariable linear regression of natural log-transformed predicted 30-year CVD risk: males

	MALES					
	Model 1		Model 2		Model 3	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p
High birth weight (HBW)*			-0.011 (-0.060, 0.039)	0.67	0.058 (-0.050, 0.165)	0.29
Low birth weight (LBW)*			0.002 (-0.072, 0.076)	0.95	0.077 (-0.059, 0.212)	0.27
MVPA at Wave I (MVPA1)	0.000 (-0.004, 0.005)	0.86			0.003 (-0.002, 0.008)	0.28
HBW × MVPA1					-0.011 (-0.023, 0.002)	**0.09**
LBW × MVPA1					-0.008 (-0.023, 0.007)	0.31
MVPA at Wave III (MVPA3)	-0.005 (-0.011, 0.001)	0.13			-0.005 (-0.013, 0.002)	0.18
HBW × MVPA3					0.003 (-0.012, 0.018)	0.70
LBW × MVPA3					-0.004 (-0.034, 0.025)	0.77
Age at Wave IV	0.086 (0.076, 0.096)	**0.00**	0.087 (0.077, 0.097)	**0.00**	0.086 (0.077, 0.096)	**0.00**
Black race*	0.028 (-0.032, 0.089)	0.36	0.025 (-0.037, 0.086)	0.43	0.028 (-0.032, 0.088)	0.36
Asian race*	-0.035 (-0.143, 0.073)	0.52	-0.037 (-0.144, 0.071)	0.50	-0.038 (-0.147, 0.071)	0.49
Hispanic ethnicity*	-0.003 (-0.066, 0.059)	0.92	-0.007 (-0.069, 0.055)	0.83	-0.003 (-0.066, 0.060)	0.93
Smoking at Wave I	0.126 (0.069, 0.184)	**0.00**	0.124 (0.068, 0.180)	**0.00**	0.126 (0.069, 0.184)	**0.00**
Smoking at Wave III	0.270 (0.225, 0.314)	**0.00**	0.274 (0.230, 0.318)	**0.00**	0.270 (0.226, 0.314)	**0.00**
Parent some college at W1*	-0.031 (-0.082, 0.019)	0.22	-0.032 (-0.082, 0.018)	0.21	-0.030 (-0.081, 0.021)	0.25
Parent college degree at W1*	-0.059 (-0.100, -0.019)	**0.01**	-0.061 (-0.102, -0.020)	**0.00**	-0.058 (-0.099, -0.018)	**0.01**
Household income at Wave I	0.000 (-0.001, 0.000)	0.56	0.000 (-0.001, 0.000)	0.54	0.000 (-0.001, 0.000)	0.54
Constant	-0.096 (-0.386, 0.194)	0.51	-0.120 (-0.403, 0.162)	0.40	-0.117 (-0.406, 0.172)	0.43

Model 1: excludes BW variables and interaction terms. Model 2: excludes MVPA variables and interaction terms. Model 3: fully adjusted model with BW indicator variables, MVPA variables, BW×MVPA interaction terms, age at Wave IV, race/ethnicity, smoking at Wave I, smoking at Wave III, educational attainment, and household income at Wave IV. Analytic sample *n*=3881 males. * indicator variable. MVPA: moderate-to-vigorous physical activity.

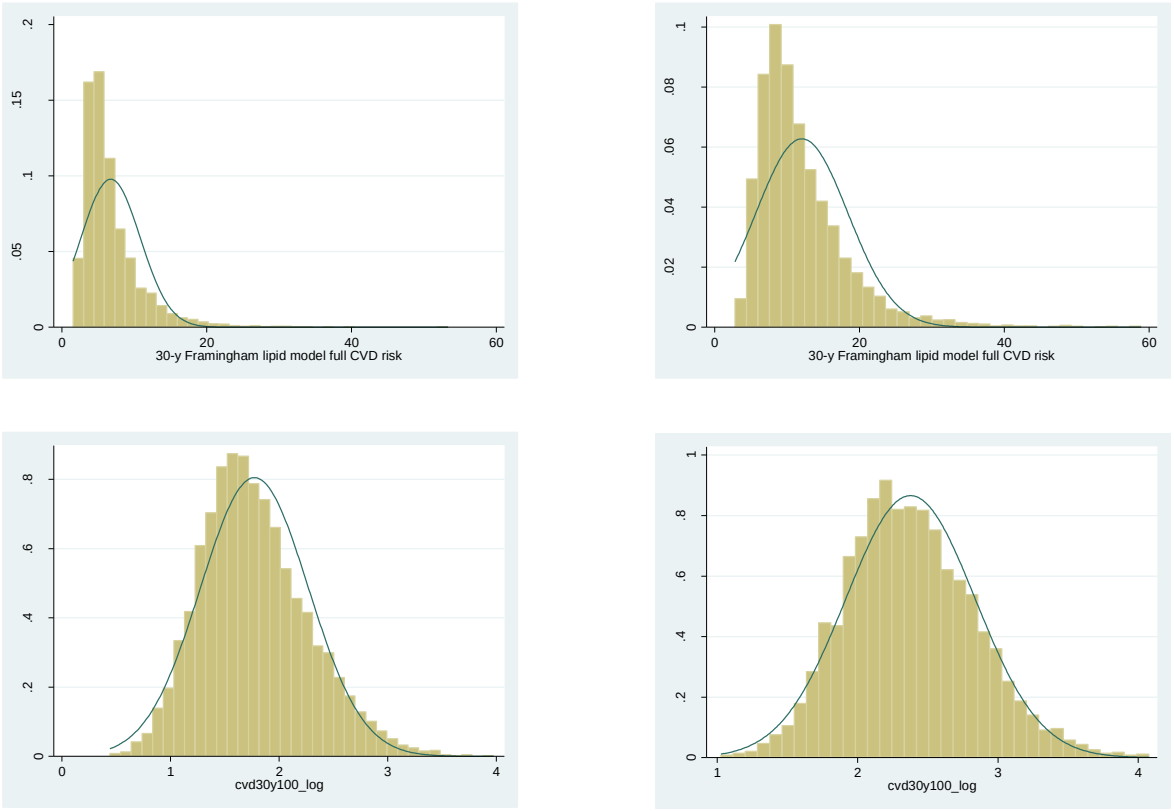

Figure A1. Histograms of CVD risk variable untransformed (top) and natural-log transformed (bottom); females at left and males at right