Preventive Medicine 84 (2016) 69–75

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Birth weight and adult cardiovascular risk factors using multiple birth status as an instrumental variable in the 1958 British Birth Cohort

Man Ki Kwok [a], Shiu Lun Au Yeung [a], Gabriel M. Leung [a], C. Mary Schooling [a,b,*]

[a] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region
[b] City University of New York and Hunter College, School of Public Health, New York, United States

ARTICLE INFO

Available online 31 December 2015

Keywords:
Adult
Cohort studies
Multiple births
Birth weight
Cardiovascular diseases

ABSTRACT

Background. Birth weight is classified as a risk factor for cardiovascular disease by the World Health Organization, but appropriate preventive interventions remain unclear because the observations have not been confirmed in experiments and appear to be contextually specific.

Methods. Using 9452 participants of the 1958 British Birth Cohort at age 42 years in 2000 (58% follow-up), we examined the credibility of multiple birth status as an instrumental variable (IV) for birth weight and, if appropriate, use it to obtain less confounded estimates of the associations of birth weight with cardiovascular disease risk factors including self-reported height, body mass index and hypertension than conventional regression in 2014.

Results. Multiple birth (203 twins and 6 triplets) was associated with older maternal age, but not with paternal occupation or maternal smoking. Multiple births had lower birth weight-for-gestational age z-score. Multiple birth status was not directly associated with height, BMI or hypertension. Using IV estimates birth weight-for-gestational age z-score was not clearly associated with height (0.99 cm, 95% confidence interval (CI) −0.27, 2.25), body mass index (BMI) (0.42 kg/m^2, 95% CI −0.17, 1.01) or hypertension (risk ratio 0.82, 95% CI 0.54, 1.23) adjusted for maternal age, with a first-stage F statistic of 145.3 from IV analysis.

Conclusions. Multiple birth status is a credible IV for obtaining a less confounded estimate of the association of birth weight with height, BMI and blood pressure. Such analysis suggests that birth weight may be spuriously related to height, BMI and blood pressure, and thus not an effective target for intervention.

Introduction

The World Health Organization has classified low birth weight as a risk factor for cardiovascular disease (World Health Organization, 2013), which should be a key target for intervention if it is causal. Birth weight, as well as size at postnatal growth phases, is a reflection of multiple underlying exposures. Identifying which growth phase is implicated in cardiovascular disease development would enable targeting at a more focused intervention window. If birth weight plays a role on future cardiovascular risk, intervening modifiable factors affecting birth weight could improve population cardiovascular health. Yet controversy remains as to whether birth weight is simply spuriously related to cardiovascular disease and its risk factors with the observed association due to confounding by other causal factors (Bhutta, 2013). The fetal origins hypothesis stemmed from observations of geographical correlations of neonatal mortality with ischemic heart disease mortality half a century later in Britain (Barker and Osmond, 1986), and observations of lower birth weight associated with higher blood pressure in a British birth cohort (Wadsworth et al., 1985). Fetal under-nutrition has been hypothesized to program metabolism for life (Barker, 1997), although the exact programming mechanisms are not fully understood, but could be due to the development of fewer nephrons (Osmond and Barker, 2000) or to an epigenetic effect (Hanson and Gluckman, 2005). Observationally, lower birth weight is associated with hypertension (Huxley et al., 2000) and cardiovascular mortality (Risnes et al., 2011).

Experimental evidence concerning the role of birth weight from randomized controlled trials in humans is lacking because birth weight is difficult to change via maternal supplementation (Mathews et al., 1999). As such, most evidence comes from observational studies in developed Western populations where socioeconomic position (SEP) is positively associated with birth weight (Blumenshine et al., 2010) and negatively associated with cardiovascular disease and its risk factors (Colhoun et al., 1998). Such observations are inevitably open to residual

Abbreviations: BMI, body mass index; CI, confidence interval; IV, instrumental variable; IVA, instrumental variable analysis; MGMM, multiplicative generalized methods of moment; SEP, socioeconomic position; UK-WHO growth chart, United Kingdom-World Health Organization growth chart; z-score, standard deviation score; 2SLS, 2-stage least squares.

* Corresponding author at: School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, G/F, Patrick Manson Building (North Wing), 7 Sassoon Road, Hong Kong Special Administrative Region. Tel.: +852 3917 6732; fax: +852 3520 1945.
E-mail address: cms1@hkucc.hku.hk (C. Mary Schooling).

http://dx.doi.org/10.1016/j.ypmed.2015.12.016
0091-7435/

confounding by SEP and other related attributes given the difficulty of comprehensively measuring all aspects of SEP (Brion, 2010). Evidence from the limited number of studies available from non-Western settings is less consistent. Higher birth weight was associated with higher adult body mass index (BMI) but lower systolic blood pressure in prospective birth cohort studies from the economically developing settings of Brazil, Guatemala, India, Philippines and South Africa (Adair et al., 2013). Higher birth weight was unrelated to systolic blood pressure, but was associated with abdominal adiposity, in a relatively affluent birth cohort (from New Delhi) in the economically developing setting of India (Fall et al., 2008). Birth weight had U-shaped associations with hypertension and abdominal adiposity in a cross-sectional study in Chinese adults (Tian et al., 2006). This lack of replication in non-Western settings suggests that observed associations are contextually specific potentially casting doubt on causality (Brion, 2010).

In this situation where evidence from trials intervening on birth weight successfully is unavailable, and discrepancies across settings indicate that confounding may underlie the observed associations, an instrumental variable (IV) analysis (IVA) with a credible IV provides an alternative means to generate a potentially less confounded estimate from observational data. IVA exploits the part of the variation in birth weight predicted by multiple birth status but is unlikely to be confounded. While conventional regression can adjust for measured confounders, residual confounding is still possible because of imprecise measurement or incomplete assessment. As such, IVA, using an instrument that is not confounded by the same set of measured confounders as birth weight, is less subject to the residual confounding that often biases observational regression estimates. Moreover, IV analysis using multiple birth status can take advantage of naturally occurring difference in birth weight and thus minimizes possible unmeasured confounding.

Before the widespread use of assisted reproduction, multiple births were largely a random genetic event (Bortolus et al., 1999). Although previously observed associations for birth weight are primarily based on singletons (Huxley et al., 2002), no empirical evidence suggests that the fetal programming of lower birth weight in twins is different from that in singletons due to factors associated with twinning such as zygosity, placentation and shorter gestation (Morley, 2005). Given twins or triplets have lower birth weight than singletons (Garite et al., 2004), multiple birth status has been used as a proxy of suboptimal fetal conditions, but has not been found directly associated with cardiovascular disease (Oberg et al., 2012). In long-term developed Western populations, where the effect of birth weight is difficult to disentangle from inter-generational influences (Emanuel et al., 2004), socioeconomic patterning (Spencer, 2004), and maternal attributes, such as smoking and preeclampsia (Huxley et al., 2002), multiple birth status is less susceptible to these potential confounders. Older mothers are more likely to have multiple births perhaps due to rising gonadotropins with age (Lambalk et al., 1998), but multiple births are not clearly associated with maternal size (Bortolus et al., 1999) or maternal smoking (Kallen, 1998). A case study found lower rates of multiple births in Japan during wartime (Nakamura et al., 1990), however higher rates of multiple births were observed in France along with older age at childbearing due to postponement of marriage by war (D'Addato et al., 2006). Moreover, vitamin supplement intake in early pregnancy is unrelated to multiple births (Li et al., 2003). As such, multiple birth status is unlikely to be affected by maternal nutrition during pregnancy or subsequent complications such as preeclampsia. Multiple births has been recently shown to be associated with higher SEP possibly due to increased access to assisted reproduction (Dawson et al., 2015). However, no clear socioeconomic patterning of multiple births was reported in Britain in earlier years (Nylander, 1981; Maher and A, 2004). Fig. 1 shows the hypothesized relations in a directed acyclic graph. To clarify the potential role of birth weight in cardiovascular disease, and thereby inform interventions to prevent cardiovascular disease globally, we used multiple birth status as an instrumental variable for birth weight. First, we assessed the credibility of multiple birth status as an IV for birth weight and then used multiple birth status as an IV to estimate the association of birth weight with adult cardiovascular risk factors including height, BMI and hypertension in a birth cohort from a long-term developed Western population, i.e., the 1958 British Birth Cohort study, where births predate the use of assisted reproduction and the distribution of birth weight is similar to that in contemporary Western populations (Cole, 2000).

Materials and methods

Ethics statement

The survey of the 1958 British Birth Cohort at 42 years obtained ethics approval from the North Thames Multi-centre Research Ethics Committees. This specific analysis of publicly available de-identified data does not require ethics approval.

Data source

The 1958 British Birth Cohort (National Child Development Study) is a population-based study of 17,416 infants born in England, Scotland and Wales in the week of March 3 to 9, 1958 (98% of all births), as described in detail elsewhere (Power and Elliott, 2006). The study was initially established to investigate the effects of social and obstetric factors on stillbirth and neonatal mortality. Birth and maternal characteristics and family SEP was collected by

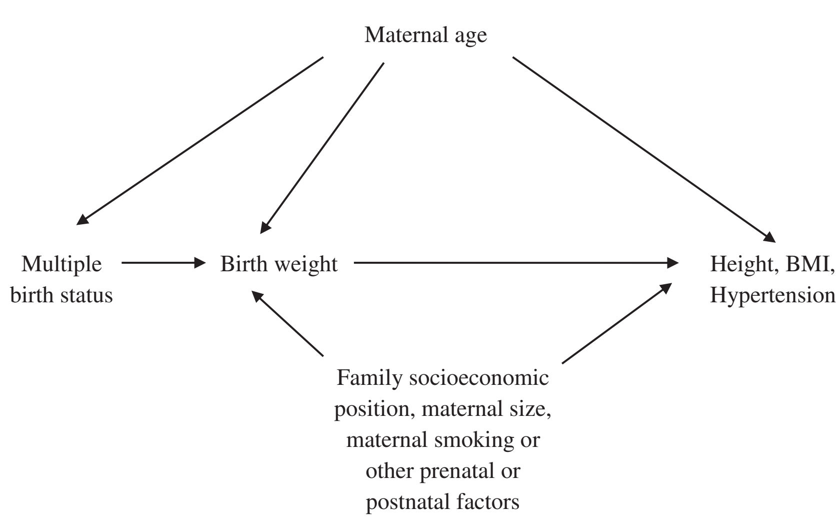

Fig. 1. Directed acyclic graph for the assessment of the association of birth weight with height, BMI and hypertension using multiple birth status as an instrumental variable.