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Associations of mortality with own height using son's height as an instrumental variable

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ABSTRACT

Height is associated with mortality from many diseases, but it remains unclear whether the association is causal or due to confounding by social factors, genetic pleiotropy,[1] or existing ill-health. The authors investigated whether the association of height with mortality is causal by using a son's height as an instrumental variable (IV) for parents' height among the parents of a cohort of 1,036,963 Swedish men born between 1951 and 1980 who had their height measured at military conscription, aged around 18, between 1969 and 2001. In a two-sample IV analysis adjusting for son's age at examination and secular trends in height, as well as parental age, and socioeconomic position, the hazard ratio (HR) for all-cause paternal mortality per standard deviation (SD, 6.49 cm) of height was 0.96 (95% confidence interval (CI): 0.95, 0.96). The results of IV analyses of mortality from all causes, cardiovascular disease (CVD), respiratory disease, cancer, external causes and suicide were comparable to those obtained using son's height as a simple proxy for own height and to conventional analyses of own height in the present data and elsewhere, suggesting that such conventional analyses are not substantially confounded by existing ill-health.

1. Introduction

Predominantly inverse associations of height with all-cause mortality have been found in a large number of studies in developed countries (Davey Smith et al., 2000; Engeland et al., 2003; Jousilahti et al., 2000; Koch, 2011; Song et al., 2003; Song and Sung, 2008). This appears to be driven by inverse associations of height with cardiovascular disease (CVD) and respiratory disease mortality (Cook et al., 1994; Gunnell et al., 2003; Lawlor et al., 2004; Lee et al., 2009; Paajanen et al., 2010), and partly counteracted by positive associations with many forms of non-smoking related cancers (Batty et al., 2010; Green

Abbreviations: IV, instrumental variable; HR, hazard ratio; SD, standard deviation; CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; SEP, socioeconomic position; CHD, coronary heart disease.

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[1] Pleiotropy is the influence of one gene on multiple phenotypic traits.

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et al., 2011; Gunnell et al., 2001). The mechanisms underlying these associations, however, are unclear. They might be explained by residual confounding, for example by socioeconomic position (Batty et al., 2006; Davey Smith et al., 2000; Gunnell, 2002; Leon et al., 1995), by genetic variants with pleiotropic effects (Silventoinen et al., 2003), or confounding due to existing but undiagnosed illness (sometimes also referred to as reverse causality). Beyond confounding, a range of possible biological mechanisms have been proposed. For example, the greater lung capacity of taller people might be protective against respiratory disease (Batty et al., 2006; Davey Smith et al., 2000), while the increased risk of most cancers in taller people might be due to the increased number of cells available to become cancerous (Albanes and Winick, 1988). It is important to establish whether an association is causal before exploring the plausibility of different biological mechanisms which could provide insights into the prevention of disease.

Various approaches have been taken to quantify, or to adjust for, the influence of confounding on these associations. Studies of monozygotic and dizygotic twins (Lundqvist et al., 2007; Silventoinen et al., 2003, 2006) can begin to establish whether genetic or shared environmental characteristics explain the associations. The study of socially homogeneous groups (McCarron et al., 2002; Murray, 1997; Okasha et al., 2000) has reduced the influence of social confounding, at the cost of a loss of generality. To avoid confounding due to ill-health and the resultant shrinkage, several studies have used a subject's maximum height, or excluded deaths occurring in the first few years after measurement (Batty et al., 2010; Leon et al., 1995; McCarron et al., 2002). These studies suggest that all of the listed sources of confounding may apply for some causes of mortality in some circumstances, but adjustment for confounders has always been imperfect, and many studies have been restricted to particular causes of mortality, in limited study samples.

Here, we take another approach to adjustment for confounding, using offspring height as an instrumental variable (IV) for assessing the causal effect of own height on all-cause and cause-specific mortality. The adult height of a subject's offspring is strongly correlated with the subject's own height, but is unlikely to be substantially influenced by the subject's existing, but undiagnosed illness. The latter assertion is untestable, but we argue that it is plausible since (i) much of the variation in height is genetically determined and (ii) most parental illness and death occurs after children reach adult height. Thus, we can use offspring height as an IV for own height, under the assumption that this will better control for confounding by existing illness, though we acknowledge that this approach will not fully control for confounding by socioeconomic, lifestyle or genetic characteristics which are shared by parents and offspring. We have previously used this approach to examine the causal effect of BMI on all-cause and cause-specific mortality (Davey Smith et al., 2009).

2. Study population and data linkage

The unique national identity numbers and dates of birth of all 1,629,396 boys born in Sweden between 1951 and 1980, and of their biological parents, were extracted from the Swedish Multi-Generation Register (Fig. 1). The sons' identity numbers were used to obtain their height, where available, from records of conscription examinations between September 1969 and December 2001. Weight and blood pressure were also available from most examinations, and smoking habits were available from 29,541 examinations, mostly in 1969 or 1970. Conscription examinations were compulsory for young Swedish men during the study period, except those with severe handicap or chronic disease, and took place at a mean age of 18.3 years (range 16–25, with 91% aged 17 or 18). The 16% with missing data were primarily due to accidental loss following changes in data management at the conscription authority. To avoid pseudo-replication within families, only one son from each parent was retained in the data set. Sons to be retained were randomly chosen, except that the same son was retained for both of his parents whenever possible.

Parents' identity numbers were matched to the Swedish Cause of Death Register, providing the underlying cause of death for all deaths between 1961 and 2004. Emigration records were also available, allowing the assumption that parents not dead or emigrated by 31 December 2004 were still alive at this time. The conscription examination records included data for 71,836 father–son pairs, with fathers having undergone examinations between 1969 and 1991. The Swedish Population and Housing Census provided data on parents' educational level and occupational socioeconomic index (SEI) in 1970 and 1990. We took the higher of the 1970 and 1990 values for educational level and classified it into five levels: <9 years; 9–10 years; full secondary; higher; and missing (2% of mothers and 5% of fathers). We also classified parents according to five mutually exclusive categories of occupational SEI: high/intermediate non-manual; low non-manual; skilled manual; unskilled manual; and other/missing. We used the 1970 value for parents born before 1935 and the 1990 value for parents born later. 27% of mothers fell into the other/missing category, comprising 2% missing data and 25% others (including housewives, farmers ($<1\%$) and part-time workers). 20% of fathers were categorised as other/missing, comprising 2% missing, 4% farmers and 14% others. Cause-specific deaths (see Table A1 in Appendix) were defined using the international classification of diseases codes (ICD versions 7–10) from the cause of death register, with some causes being subsets of others (for example, site specific cancers were subsets of cancer as a whole), in a similar manner to Davey Smith et al. (2009).

Our final main analyses were conducted on 997,110 father–son pairs and 1,013,293 mother–son pairs, with additional analyses that used father's height as well as son's height conducted on 71,836 father–son pairs (Fig. 1).

3. Statistical analysis

Son's height was adjusted for secular trends and the effect of age at examination by taking residuals from a regression of son's height on cubic splines of age at examination and date of birth (7 knots at percentiles of 2.5,