Insights From the Positive Association of Height With Incident Venous Thromboembolism

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Height and Venous Thromboembolism

Zöller et al[1] clearly show height positively associated with incident venous thromboembolism (VTE) in both men and women using an observational design and a cosibling design in a very large study, including a sizeable segment of the Swedish population, that is, all males born 1951 to 1992 without previous VTE and all first time pregnant women from 1982 to 2012. Despite the large size of the study,[1] the observational design is open to bias from confounding by common causes of height and VTE. Inevitably, in a study making cost-effective use of invaluable Swedish registry data, Zöller et al[1] were unable to adjust for all potential confounders leaving the study open to bias from residual confounding from unmeasured attributes affecting both height and VTE. For example, they used participant's educational level as a confounder[1] instead of all aspects of parental socioeconomic position which might not fully account for confounding by such an influential, multidimensional attribute as parental socioeconomic position. Residual confounding by parental socioeconomic position could in this instance partially obscure any harmful effects of greater height, meaning that the observational estimate might underestimate any harmful effects of height. Zöller et al[1] also adjusted for family history of VTE and body mass index. Family history and body mass index are probably not confounders, because they may cause VTE, they are unlikely to determine height, although height might determine body mass index. As such, the adjusted estimates have also been adjusted for potential mediators, which might attenuate any harmful effects of height, meaning that the observational estimate might be an underestimate. In this situation, the cosibling design is particularly helpful because it makes different assumptions. The cosibling design essentially compares siblings, which automatically controls for measured and unmeasured confounders shared by siblings, such as parental socioeconomic position and attributes of the extended family and of the family going back over generations. The cosibling design is however open to biases from measurement error of height and confounding by factors that differ between siblings,[2] particularly confounders that are less shared than the exposure.[2] Height is easy to measure and was taken from routine measurements.[1] Family socioeconomic position is a key shared potential confounder for height and VTE, whereas factors such as birth order, relationships within the family, childhood lifestyle preferences, and genetics may differ between siblings, but are less likely to be influential confounders. Similar estimates from the 2 different study designs with these different potential biases give greater confidence, although more credence might be given to the cosibling design.

See Article by Zöller et al

Findings by Zöller et al[1] are also consistent with a recent Mendelian randomization study showing that men and women with genetically predicted taller height were more vulnerable to VTE,[3] although the findings were not completely robust to sensitivity analysis.[3] Mendelian randomization studies take advantage of genetic differences to proxy the exposure because genetic endowment represents a random reassortment at conception, thus providing randomization of the exposure similar to that in a randomized controlled trial.[4] As such, Mendelian randomization studies are less vulnerable to confounding but have other assumptions that are difficult to verify. Mendelian randomization studies require reliable genetic predictors of the exposure, no unmeasured factors confounding the association of genetic predictors of the exposure with the outcome, and that the genetic predictors of the exposure act on the outcome solely via the exposure. Nevertheless, Mendelian randomization studies have been very helpful in clarifying causes of cardiovascular disease, distinguishing between valid and invalid targets of intervention, and even foreshadowing the results of key cardiovascular disease randomized controlled trials, such as predicting the results of the VISTA-16 trial (Evaluation of Safety and Efficacy of Short-term A-002 Treatment in Subjects with Acute Coronary Syndrome) of Varespladib.[4]

Taken together, the consistent evidence to date from these 3 different study designs, that is, observational, cosibling,[1] and Mendelian randomization,[3] with different assumptions for validity strongly suggests a real rather than artifactual causal effect of greater height increasing VTE. Given that height is usually associated with longevity,[5] these findings clearly require some explanation.

Height and Health

Overall taller height has positive effects on many attributes including education, income, and occupation,[6] as well as being associated with lower mortality,[5] at both the individual[7] and aggregate levels. Figure shows the strong positive correlation of country average height with life expectancy by sex. However, the positive relation of height with health is not

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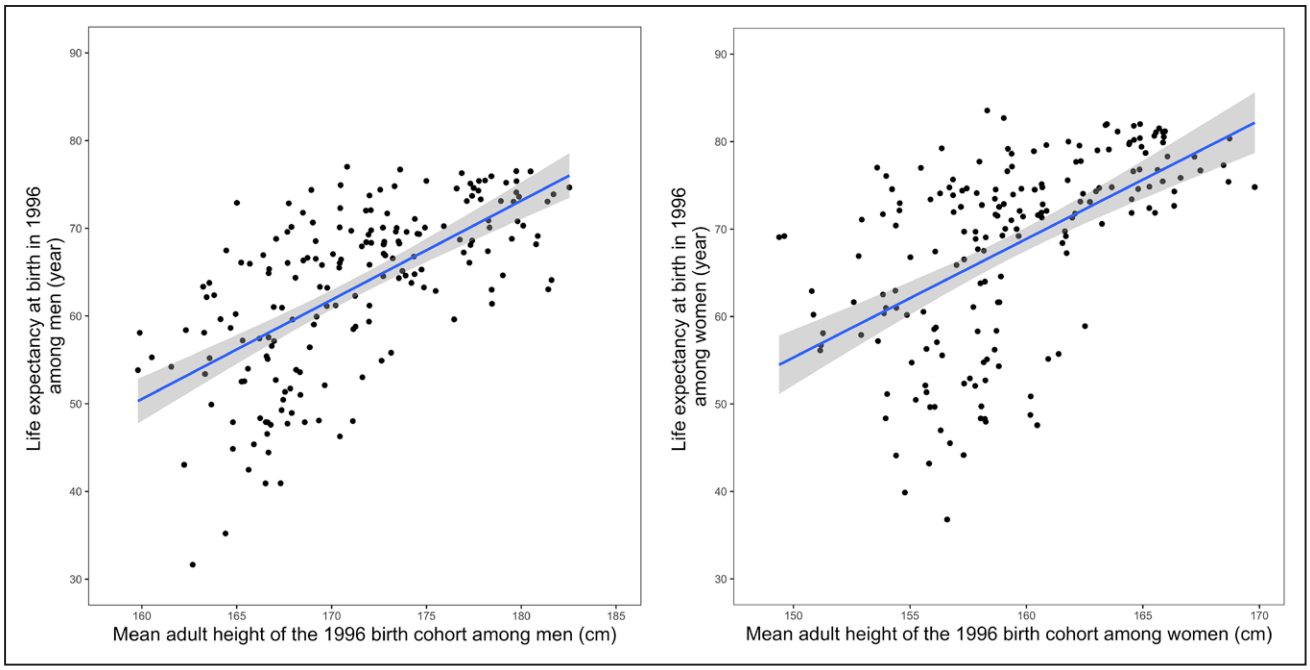

Figure. Life expectancy at birth in 2014 (World Bank) against adult height of the 1996 birth cohort by country[5] for men (**left**) and women (**right**).

consistent for all causes of death. Associations also may also be specific to 1 component of height, that is, leg length or trunk length. Leg growth, particularly in girls, occurs before puberty and so leg length represents prepubertal exposures, whereas trunk growth continues into puberty and so may more represent adolescent exposures.[8] More fundamentally, it is not entirely clear what height represents, why it matters to health or what are the implications for interventions. Specifically, both the attributes of height that underlie this particular observation on greater height likely causing VTE and how this information might relate to a more general explanation for the overall pattern of effects of height on health are unknown.

Observationally, height is inversely associated with most major cardiovascular diseases, including coronary artery disease, stroke, and heart failure, but positively associated with some specific cardiovascular diseases, including pulmonary embolism, aortic aneurysm,[7] VTE,[9] and atrial fibrillation.[10] Height is also inversely associated with mortality from chronic obstructive pulmonary disease and related conditions, mental disorders, liver disease, and some infection-related cancers, such as stomach and oral cancer,[7] but positively associated with mortality from most lifestyle-related cancers, such as cancers of the skin, colorectum, and lung, and endocrine-related cancers, including cancers of the breast and prostate.[7] However, Mendelian randomization studies suggest that only some of these associations are causal. Greater height associated with a lower risk of coronary heart disease has been replicated in Mendelian randomization studies,[11] but an effect of height on stroke was not substantiated.[12] Future Mendelian randomization studies will undoubtedly provide further disease-specific clarification.

As regards the role of components of height, a previous observational study found leg length rather than trunk length explained the association of greater height with higher risk of VTE, with possibly a stronger relation in women than men.[9] Zöller et al[1] do not have information on leg length and trunk length in their study, so they could not generate further insight by ascertaining whether longer legs or a longer trunk or both were associated with VTE using a cosibling study design. Some indications exist that trunk length is more strongly positively associated with some markers of coagulability than leg length.[13] In contrast, inverse associations of height with coronary heart disease seem to be driven by leg length rather than trunk length.[14] Mendelian randomization studies have not clarified the role of leg length versus trunk length in any disease. Zöller et al[1] postulate that some of the association of height with VTE could be mediated by attributes of longer legs, such as greater venous surface area, possibly more valves or more damage to the vessel walls, which is quite possible. However, height in men was not only associated with VTE in the legs, but with all types of VTE,[1] suggesting that a more general explanation for this hypercoagulability is required going beyond the attributes of legs to a more comprehensive explanation, ideally with actionable targets.

Height as an Indicator of Early Exposures

Height is partially a reflection of environmental exposures from the conception to the completion of growth. Environmental insults, such as infections, air pollution, inadequate nutrition, and stress, may all preclude achieving genetic height potential, as well as increasing the risk of disease in adulthood. For example, air pollution in early life could impair both linear growth and lung development resulting in lifelong vulnerability to respiratory disease and thereby cardiovascular diseases. Similarly, an environment with a higher infectious disease burden might result in both more frequent infections impairing linear growth and a higher chance of catching the particular infections that cause cancer in later life, thereby

generating the observed associations of shorter height with infection-related cancer. Alternatively, limited conditions might preclude investment in a robust phenotype resistant to chronic diseases. However, these explanations are difficult to reconcile with a positive effect of height on VTE. These explanations are also hard to reconcile with associations that may differ for leg and trunk length because environmental exposures for any given individual are likely to remain broadly similar from conception to the completion of growth. As such, a mechanism whereby the same exposures may be embodied differently at different growth phases is required.

Biological drivers of linear growth include growth hormone/insulin-like growth factor 1, thyroid hormone, and sex steroids, with some playing a greater role at some growth phases than others. For example, sex steroids play a role mainly during the mini-puberty of infancy and again during puberty. As such, the same exposure may operate through different biological mechanisms at different growth phases with potentially different long-term effects on health. Effects of growth hormone/insulin-like growth factor 1 on VTE have not been clearly established. However, people with isolated growth hormone deficiency resulting in markedly lower insulin-like growth factor 1 do not seem to be at higher risk of cardiovascular disease,[15] although a specific effect on VTE cannot be entirely excluded, because of the rarity of the condition. Thyroid hormone, as dextrothyroxine, was not beneficial in the Coronary Drug Project, and the relevant trial arm was discontinued, but the possibility of an effect on specifically VTE remains. In contrast, sex steroids are well-known causes of VTE. Oral contraceptives have been known to cause VTE since the 1960s from shortly after their introduction. Meta-analysis of randomized controlled trials of hormone replacement therapy in older women have confirmed that estrogen increases VTE.[16] Consistent with this potential pathway, greater height in women is also associated with hormone-related cancers such as breast cancer,[7] suggesting that height could possibly operate via hormone levels. The risk of VTE on testosterone has recently been highlighted by Health Canada and the US Food and Drug Administration.[17] Meta-analysis of randomized controlled trials is also suggestive of a higher risk of VTE on testosterone, but the evidence is too limited to be definitive.[17] Consistent with this potential pathway, testosterone also raises one of the key factors in the coagulation cascade, that is, thromboxane A_2,[18] providing a mechanism for hypercoagulability. Height is also positively associated with testosterone in men,[19] suggesting that environmental conditions which enable greater linear growth may also enable higher levels of lifelong androgens. This explanation may also extend to other types of cardiovascular disease associated with greater height, that is, aortic aneurysm[7] and atrial fibrillation.[10] Antiandrogens have been suggested as a treatment for abdominal aortic aneurysm based on animal evidence.[20] Androgens also seem to promote atrial fibrillation in animals.[21] However, this explanation does raise the question as to why taller height is protective for coronary artery disease, particularly given that venous and atherosclerotic cardiovascular disease may share risk factors.

Height Within Evolutionary Biology

More generally, as another source of additional insight, the positive association of height with VTE can most easily be conceptualized within the well-accepted evolutionary biology theory of life history trade-offs, where growth and reproduction trade-off against longevity,[22] potentially through factors promoting height and fertility at the expense of lifespan. From this perspective, greater height and reproductive capacity would be expected to be harmful, although the evidence in humans is limited. A recent genetic study in humans showed genetic selection in favor of both fertility and coronary heart disease.[23] However, that theory is not consistent with greater height protecting against coronary artery disease,[11] although the association could be confounded by socioeconomic position over generations. Historically, it has taken at least 6 generations for people to reach their full genetic height potential.[24] Alternatively, the association could be mediated by genetically predicted taller height leading to socioeconomic advantage.[6] Despite, the lack of extensive evidence in humans consistent with this evolutionary biology perspective, implicitly or explicitly it is informing some of the newer approaches to cardiovascular disease prevention and treatment, such as interest in diets that mimic fasting,[25] and the identification of novel drug targets.[18]

Conclusions

All in all well-conducted study by Zöller et al[1] clearly shows that taller height plays a role in VTE, consistent with results from Mendelian randomization,[3] giving these results high credibility. These apparently paradoxical findings could simply be explained by attributes of longer legs. Similar observations for pulmonary embolism,[7] aortic aneurysm,[7] and atrial fibrillation[10] suggest that these are not all chance findings but require a more comprehensive explanation placing VTE within a holistic model of cardiovascular disease whose application could lead to new interventions.[18] Moreover, any such explanation may also have broader implications relevant to the potential use of early adult height as an indicator of sustainable development[5] and the Sustainable Development Goals aiming to reduce the prevalence of stunting among children under 5 years of age.

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Disclosures

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