

Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis

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Aims

The aim of this study was to assess the relationship between short stature and coronary heart disease (CHD) morbidity and mortality.

Methods and results

We performed a systematic search from MEDLINE, PREMEDLINE, and All EBM Reviews as well as from a reference list of relevant articles. We used SPICO (Study design, Patient, Intervention, Control-intervention, Outcome) criteria. The methodological quality of studies was analysed by modified Borghoust criteria. From a total of 1907 articles, we selected 52 studies comprising population-based follow-up studies and patient cohorts followed after a CHD event, as well as case-control studies with height either as a continuous or categorical variable, totalling 3 012 747 individuals. The short ones were below 160.5 cm and tall ones over 173.9 cm on average. Among the shortest height category, the relative risks were 1.35 (95% CI 1.25–1.44) for all-cause mortality, 1.55 (1.37–1.74) for all cardiovascular disease (CVD) mortality, 1.49 (1.33–1.67) for CHD, and 1.52 (1.28–1.81) for myocardial infarction when compared with those within the highest height category. The mean relative risk was 1.46 (1.37–1.55). Short stature was associated with increased cardiovascular morbidity and mortality in both genders.

Conclusion

The relationship between short stature and CVD appears to be a real one. On the basis of comparison, adults within the shortest category had an ~50% higher risk of CHD morbidity and mortality than tall individuals.

Keywords

Short stature • Height • Coronary heart disease • Systematic review • Meta-analysis

Introduction

History

The first report on the inverse association between coronary heart disease (CHD) and height was published in 1951.¹ It was found that the average height of males hospitalized for myocardial infarction (MI) prior to the age of 40 was 5.08 cm lower (170.2 cm) than the average height of the non-hospitalized control group (175.3 cm). Since then, the association between short stature and cardiovascular diseases (CVDs) has been dealt with in more than 1900 papers according to database search. Many reports agree with Gertler *et al.*,^{2–12} but this association was also considered a misconception, as several large epidemiologic follow-up studies^{3,13–15} showed no association between height and CHD risk. It has even been suggested^{16,17} that racial factors may

determine the outcome, e.g. the shorter populations such as southern Europeans have lower death rates from CHD and all causes compared with, for example, the taller northern Europeans. Although seven reviews have been published,^{16–22} no systematic meta-analysis has been done on this topic.

The reasons for a systematic review

In this paper, we have performed, for the first time, a systematic review of studies reporting on the association between adult height and CHD events. What makes it difficult to investigate this association is that the literature deals with various populations and outcomes as well as different height criteria within various study designs. Some studies start with healthy people and follow their outcome in relation to their height, whereas other studies follow patients by stature after a CHD event. Thirdly, there are

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case-control studies that comprise coronary artery disease patients and healthy controls defined by height, with varying outcomes and treatments. These studies also differ in the way they take the effect of known CHD risk factors into account, such as age, sex, smoking, lipid disorders, and diabetes—or whether they include any of these as confounding factors in their analyses. This is important, since in many papers the association between height and CHD often disappears when adjusted for all other factors. The most striking obstacle was, however, the use of various height categories.

Article quality was assessed by Quality of Reporting of Meta-analysis criteria. The hypothesis of this study was that short height is associated with increased CHD risk. We decided to compare the shortest group to the tallest group instead of using a fixed height limit and calculated average heights for combined risk values from the meta-analysis.

Objectives

This systematic review addresses whether short height shows an inverse association with variable CHD endpoints, and what the magnitude of the possible risk is. The meta-analysis will also address the effect of gender on the risk of different endpoints.

Criteria for considering studies for this review

Types of studies, participants, interventions, and outcome measures

According to the SPICO (Study design, Patient, Intervention, Control-intervention, Outcome) criteria, the original *study design* had to be a systematic review, meta-analysis, randomized clinical trial, clinical trial, and cohort or case-control setting and feature a number of subjects over 200 in total. *Patients* had to be either healthy at the beginning or already having symptomatic CHD. The patient setting was considered quite helpful if there was division into men vs. women. *Intervention and control intervention* had to be continuous, with the mean height and standard deviation given to be dichotomized as short vs. tall ones or classified and, if classified, there had to be at least two classes. *Outcome* had to be defined as diagnosis of angina pectoris, ischaemic heart disease (IHD) or heart disease without MI, acute MI, or history of MI, coronary artery occlusion equal to or more than 50%, revascularization or percutaneous transluminal coronary angioplasty (PTCA), as well as all-cause mortality, CVD mortality, or CHD mortality, or in clinical trials and cohort studies, any of the previous after at least 2 years of follow-up.

An article was excluded if the previously mentioned SPICO criteria were not fulfilled, or the information was insufficient for quality assessment or further conclusions, or height was only mentioned as a confounding factor.

Search strategy for identification of studies

We aimed to identify all articles that investigated height and CHD association by performing a systematic literature search from MEDLINE, PreMEDLINE, and All EBM Reviews, search ending 6 April 2007. The detailed search strategy is included as a Supplementary material online. This systematic search from the

sources above yielded a total of 1907 articles. On 3 December 2007, we checked that there were no new articles to include.

Two reviewer authors (T.A.P. and N.K.J.O.) independently assessed the studies for eligibility without consideration of the results. In cases of distributed opinions, a third evaluator was used (P.J.K.).

We included an article if predefined SPICO criteria were fulfilled in title and abstract. A total of 68 articles were reviewed as full-text versions. Next, we excluded articles that did not report adult height but birth height (five rejected on this ground) and articles that did not use English language (three rejected on this ground). Sixty articles remained after these additional restrictions.

After the database search, we screened the reference lists of included articles, which yielded 22 new articles. Excluding reviews and overlapping cohorts at this point, the number of eligible articles narrowed from 82 to 52, from which the final synthesis was made.

These articles comprised various racial and socioeconomic groups and samples from both genders separately totalling 3 012 747 individuals comprising population-based follow-up studies of initially healthy people, patient cohorts followed after a CHD event, and case-control studies with adequately defined classification of height either as a continuous or categorical variable. *Figure 1* summarizes the systematic forwarding of the search.

Methods

One author (T.A.P) extracted data from a previously designed Excel database see (Supplementary material online, *Table S1*). Completed data forms were checked for discrepancies by two authors (N.K.J.O. and P.J.K.).

Systematic review

We decided to do subgroup analyses by first extracting the data of those articles that reported risk ratios (RRs). If RRs were reported for the tallest group, we changed them to represent RRs for the shortest group. If RRs were not reported, but cross-tabulation for RR calculation was possible, we used the tallest group as the reference group and calculated RRs for the shortest group.

When odds ratio (OR) was reported for the tallest group, we used the following calculation: $RR = OR/[1 - p_c(1 - OR)]$, in which p_c is the event rate for the control group.²³ When possible, we extracted the gender-specific data because gender is one known confounding factor.

We also used ORs, hazard ratios (HRs), and other variables separately when it was impossible to calculate RRs due to the total number of individuals lacking. Thus, all 52 articles included are also evaluated in this systematic review results.

Meta-analysis

Meta-analysis was accomplished using statistical StatsDirect software. To examine the heterogeneity of the results and summarize results across various articles, we used methods suggested by DerSimonian and Laird.^{24–26} The I^2 test showed 72.1% inconsistency (95% CI 62.8–78.2%). Though we found significant within-trials and between-trials heterogeneity for the articles included in the meta-analysis, we present summary estimates based on a random effects model instead of a fixed effect model. We did not remove any of the selected studies based on heterogeneity. The Z-test for overall effect was 12.1 with $P < 0.0001$. According to bias analysis (*Figure 2*), our analysis was

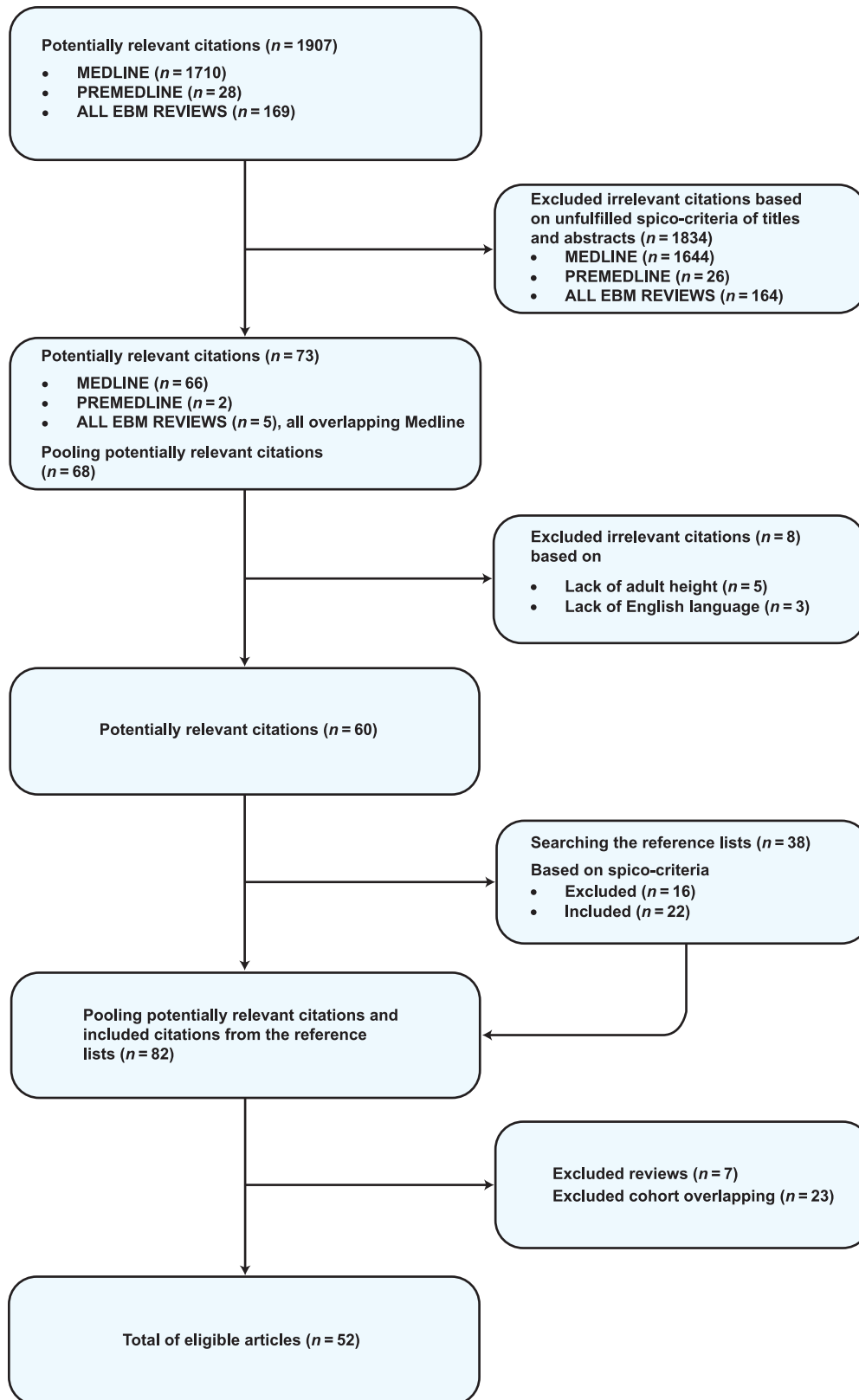


Figure 1 The Quality of Reporting of Meta-analysis flow diagram.

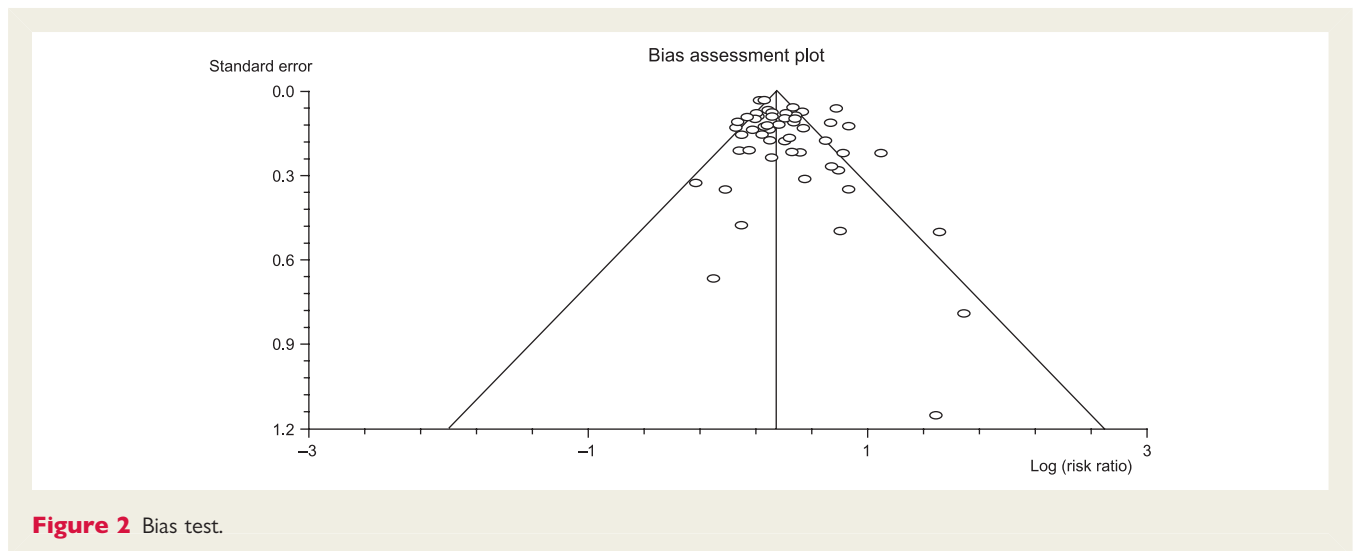


Figure 2 Bias test.

unbiased (Begg–Mazumdar: Kendall's $\tau = 0.147449$, $P = 0.1175$ and Egger: bias = 0.724877 (95% CI = -0.172388–1.622143), $P = 0.111$).

Description of studies

Supplementary material online, *Table S1*, presents the most important descriptive information for the 52 studies included in our analysis. The total number of participants included in our systematic review was 3 012 747. In the meta-analysis, it was possible to include 22 studies see (Supplementary material online, *Table S2*). From a total of 30 studies, it was not possible to extract RRs and they were analysed in the text see (Supplementary material online, *Table S3*).

Methodological quality of included studies

Criteria for the assessment of the quality of studies were modified from Borghoust *et al.*²⁷ see (Supplementary material online, *Table S4*). The quality of the studies included in the systematic review varied from 7 to 15 see (Supplementary material online, *Table S1*). The quality score was commonly low because the subcriteria of the study size (5c, 5b) or the amount of dropouts/loss to follow-up (8a) were too small, or information provided from dropouts/loss to follow-up (8b) was insufficient. There was no association between quality score and bias assessment plot scattering (data not shown).

Results

Studies included in meta-analysis

Of the 52 studies, 22^{4,5,7,11,28–45} provided adequate data for a meta-analysis based on RRs see (*Figure 3*, Supplementary material online, *Table S2*). Meta-analysis shows that risks for different kinds of cardiovascular endpoints are higher within the shortest ones when compared with the tallest height categories. The combined RR was 1.46 (95% CI 1.37–1.55). On average, the short ones were below 160.5 cm and tall ones over 173.9 cm, so the average height cut-off for short ones was 13.4 cm lower than the average height cut-off for the tall ones. When men and women were considered independently on average, short men were below 165.4 cm and short women below 153.0 cm, tall men over 177.5 cm and tall women over 166.4 cm. Height cut-offs were available for 21 articles. Only one article³³ failed to report height

cut-offs and was not taken into the calculations. Additional meta-analysis information is provided in Supplementary material online, *Table S2*.

The combined RR for all-cause mortality for short men was 1.37 (1.29–1.46) and for short women 1.55 (1.41–1.70) see (Supplementary material online, *Figures S1* and *S2*). On average, the short ones were defined to be below 161.1 cm and the tall ones over 176.0 cm and short men below 165.5 cm and short women below 153.3 cm, tall men over 178.9 cm and tall women over 163.7 cm see (Supplementary material online, *Figure S3*).

Similarly, the combined risk for all types of cardiovascular (CVD) deaths among men and women was 1.55 (95% CI 1.37–1.74) see (Supplementary material online, *Figure S4*). In line, the risk for combined CHD mortality and morbidity brought by short stature among men was 1.49 (1.33–1.67), varying between 1.10 and 4.55. In these studies, men with a height of <166.1 cm were considered short and men >176.2 cm tall. There were only three studies in women reporting a risk varying from 1.10 to 2.08 for short ones (<153.1 cm) compared with the risk among tall ones (>165.6 cm) see (Supplementary material online, *Figure S5*).

The risk of MI incidence associated with short stature was 1.52 (95% CI 1.28–1.81) for all. In these studies, the mean reported height cut-off for short males was 14.4 cm lower (164.0 cm) than the average height cut-off of tall men (178.4 cm). Similarly, there was a 14.5 cm difference between reported cut-offs for short (153.7 cm) and tall women (168.2 cm) see (Supplementary material online, *Figure S7*).

Meta-analysis subgroup results see (Supplementary material online, *Figures 1–8*) show a more detailed interpretation.

Studies not included in the meta-analysis

There were 30 studies fulfilling the SPICO criteria but not included in the meta-analysis^{2,3,6,8–10,12–15,46–65} because it was impossible to calculate RRs for absolute height cut-offs see (Supplementary material online, *Table S3*). Of these, seven studies reported RRs by variable increments of height without data on measured height.^{8,13,15,47,51,61,64} From these seven studies, we can conclude that a 5–10 cm height increase is usually linked with a reduction

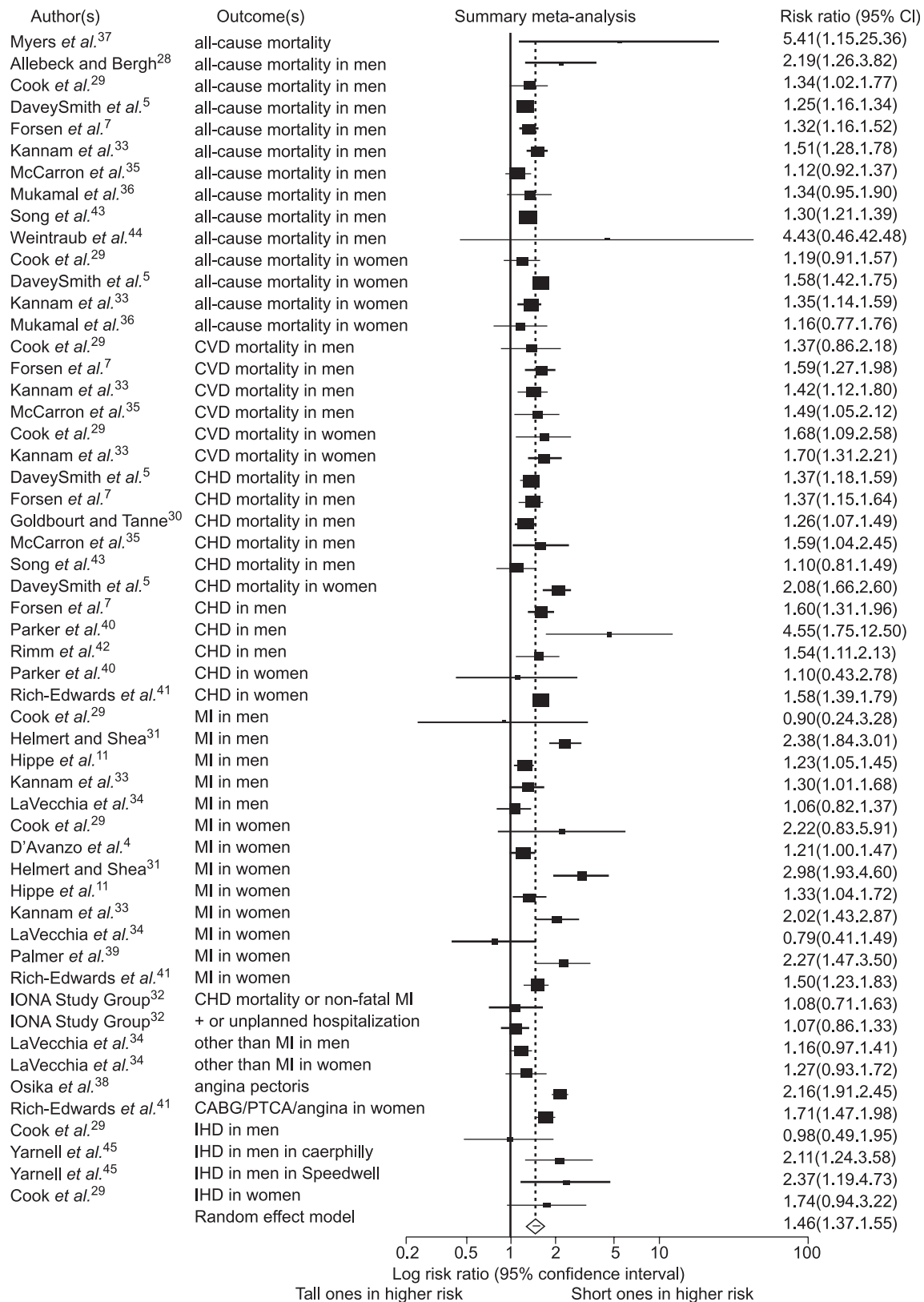


Figure 3 Meta-analysis of 22 articles.

of RR for all-cause death or CHD by 10–15% and a 30 cm decrease of height may double the risk.

Additionally, six studies reported ORs from which RRs could not be calculated.^{3,50,52,53,56,65} Incidence of non-fatal MI and CHD as well as coronary lesions $\geq 50\%$ were inversely associated with height, but 30-day or operative mortality after isolated coronary artery bypass grafting did not show significant association with height.

Furthermore, three studies reported HRs by quartiles^{14,60,63} and as with ORs, some researchers also used staircase increments of height when reporting HRs.^{6,49,55,59} An inverse association for CHD was found when height was used as a continuous variable in every study; in a twin study, discordant for height was found not only between twin individuals but also within twin pairs. Per 5 or 10 or 15 cm increase HR was inversely associated with height for fatal CVD and for fatal CHD and for all-cause mortality.

There were four studies^{2,9,10,48} reporting only statistically significant *P*-values to support statements of height being an important factor for risk of CHD.

Six studies could not be grouped at all, based on the used endpoints.^{12,46,54,57,58,62} However, reported endpoints such as operative mortality percentage after coronary artery bypass grafting (CABG), advanced coronary lesions in an autopsy study, incidence of IHD, estimated CHD mortality ratio, all-cause mortality ratio, and affirmative answer about symptoms implying coronary or peripheral atherosclerotic disease were all inversely associated with height in these studies.

Discussion

In this paper, we have addressed two questions: Is adult short stature really a risk factor for CHD events and, if it is, how big a factor is it? Our systematic review and meta-analysis show that adult short stature poses ~ 1.5 times higher risk for CHD morbidity and mortality than being a tall individual. This appears to be true both for men and women and for different kinds of endpoints. Although it has been previously hypothesized that height may possess a greater risk for men, shorter women may pose an even higher risk when other confounding factors are not taken into consideration.

Due to the heterogeneity of studies, we cannot reliably answer the question on the critical absolute height. The height cut-off points did not only differ between the articles but also between men and women and between ethnic groups. This is why we used the shortest-vs.-tallest group setting. Our strategy thereby reduced the study population pool. Based on the bias analysis, we used the random effect model, assuming that the true height value varies in different study populations. The advantage of the use of random effect model was that we did not have to remove any of the selected studies based on the variability mentioned above. We believe that this heterogeneity only strengthens the association found.

According to our modified Borghoust criteria list, the methodological quality of the articles appeared to be reasonably good on average to be used for the assessment of height as a risk factor, though most of them were originally designed for other purposes. Two of the most common methodological shortcomings appeared to be the missing number of individuals with outcome and lack of information provided for dropouts/loss to follow-up. More than half the included studies failed to fulfil these criteria.

Our systematic review has some limitations. Meta-analyses are also prone to different kinds of biases and confounding factors that are inherent to the original studies. The possibility of missing published studies also remains, though we used a large set of keywords for databases and standardized the search flow in accordance with the guidelines. Furthermore, we searched only for studies which were published in indexed journals or found from reference lists, so unpublished studies and non-indexed journals may have been partly missed. Positive results are more easily published, but in this systematic review, height was usually not the main topic of the original paper but rather was given as a demographic variable. This is why we believe that our results were not biased by positive publication bias. Only a few studies were focused to identify height as a prognostic factor.

We excluded only three studies out of the total of 1907 articles because they were not published in English. This language limit would hardly have changed the result because in these abstracts the results were parallel.

The reason(s) for short stature being a risk factor for CHD remain open for hypotheses. Most commonly, in previous studies it has been suggested that the reason behind this association could be low socioeconomic background with associated risk factors such as poor nutrition and infections resulting in poor foetal or early-life growth.^{39,66}

Nwasokva *et al.*⁵⁶ found that short men have not only a higher prevalence of coronary disease, but also a greater severity of coronary disease than tall men.⁵⁶ Also, Kortelainen and Särkioja¹² found that short stature was associated with more advanced coronary lesions.

In Physicians Health Study, there was a significant association between height and MI, but not between height and cardiovascular death.⁶⁷ Similarly, the Framingham Heart Study found no association between short stature and increased risk for all-cause or cardiovascular mortality in either sex, although shorter women had increased risk for MI.³³

In the Coronary Artery Surgery Study (CASS), surgical mortality was inversely related to the average diameter of the grafted coronary arteries in both men and women.⁶⁸ It was therefore hypothesized that the physical size of the patient, including coronary artery diameter, may predict operative mortality.⁶⁸ In recent studies using angiographic measurements, the coronary artery diameter was correlated with height and body weight.^{69,70} It could be hypothesized that smaller coronary arteries may be occluded earlier in life under similar risk conditions.

Conclusions

The relationship between short stature and CVD seems to be a real one. Adults within the shortest category had a $\sim 50\%$ higher risk of CHD morbidity and mortality compared with tall individuals. The possible pathophysiological, environmental, and genetic background of this peculiar association is not known.

Implications for practice

Height is used to calculate body mass index (BMI), which is a widely used quantity risk of CHD. The value of BMI has been recently questioned by reports showing that BMI may not associate

with the severity of CHD in angina patients with chronic kidney disease⁷¹ or may even be inversely associated.^{72,73} This has been discussed as the obesity paradox. The results of this meta-analysis suggest that height may be considered as a possible independent factor to be used in CHD risk calculations.

Implications for research

It would be interesting to explore—e.g. in autopsy series—the possibility that short stature is connected with the risk of CHD and MI through the effect of smaller coronary artery diameter, and that smaller coronary arteries may be occluded earlier in life under similar risk conditions. Recent findings on the genetic background of body height⁷⁴ suggest that inherited factors rather than speculative early-life poor nutrition or birth weight may explain the association between small stature and later-life increased risk for CHD events.

Contributions

T.A.P., N.K.J.O., P.J.K., and P.K. designed the present study. T.A.P. analysed and interpreted the data, and drafted the article. N.K.J.O., P.J.K., and P.K. interpreted and organized the data, critically revised the article and contributed to the final version.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflicts of interest: none declared.

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