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Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis

The Emerging Risk Factors Collaboration*

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Background The extent to which adult height, a biomarker of the interplay of genetic endowment and early-life experiences, is related to risk of chronic diseases in adulthood is uncertain.

Methods We calculated hazard ratios (HRs) for height, assessed in increments of 6.5 cm, using individual–participant data on 174 374 deaths or major non-fatal vascular outcomes recorded among 1 085 949 people in 121 prospective studies.

Results For people born between 1900 and 1960, mean adult height increased 0.5–1 cm with each successive decade of birth. After adjustment for age, sex, smoking and year of birth, HRs per 6.5 cm greater height were 0.97 (95% confidence interval: 0.96–0.99) for death from any cause, 0.94 (0.93–0.96) for death from vascular causes, 1.04 (1.03–1.06) for death from cancer and 0.92 (0.90–0.94) for death from other causes. Height was negatively associated with death from coronary disease, stroke subtypes, heart failure, stomach and oral cancers, chronic obstructive pulmonary disease, mental disorders, liver disease and external causes. In contrast, height was positively associated with death from ruptured aortic aneurysm, pulmonary embolism, melanoma and cancers of the pancreas, endocrine and nervous systems, ovary, breast, prostate, colorectum, blood and lung. HRs per 6.5 cm greater height ranged from 1.26 (1.12–1.42) for risk of melanoma death to 0.84 (0.80–0.89) for risk of death from chronic obstructive pulmonary disease. HRs were not appreciably altered after further adjustment for adiposity, blood pressure, lipids, inflammation biomarkers, diabetes mellitus, alcohol consumption or socio-economic indicators.

Conclusion Adult height has directionally opposing relationships with risk of death from several different major causes of chronic diseases.

Keywords Height, cardiovascular disease, cancer, cause-specific mortality, epidemiological study, meta-analysis

Introduction

Adult height is a widely available biomarker that reflects the interplay of genetic endowment and various early-life experiences and exposures (such as fetal, dietary, social and psychological circumstances).[1–5] Since the study of height could provide insights into patterns of shared and differing early

determinants of major diseases of later life, it should be informative to compare associations of adult height with subsequent risk of a wide range of disease outcomes. Previous large prospective studies have reported positive associations between height and risk of several organ-specific cancer outcomes[6–9] and they have reported negative associations between height and risk of subsequent vascular disease outcomes.[10–12] However, there have been only a few powerful studies that have examined height in a standardized manner in relation to a wide range of common and less common disease outcomes that include neoplastic, vascular, respiratory and other conditions.[13–15] Furthermore, such studies have typically lacked information on a variety of biological and other risk factors for chronic diseases needed to help determine whether there are independent relationships between height and late-onset diseases. We aimed to study associations between baseline adult height and subsequent risk of cause-specific death (as well as major vascular morbidity) by analysing data from 1 085 949 people in mostly population-based studies who were at risk for a total of 16.1 million person-years.

Methods

By mid-2012, the Emerging Risk Factors Collaboration (ERFC) had collated and harmonized individual participant data from 130 population-based prospective studies that have included a total of 2.2 million participants monitored during ~30 million person-years at risk for cardiovascular disease outcomes and cause-specific mortality.[16] The initial studies of this collaboration have reported on lipid, inflammation and glycaemia biomarkers in relation to major vascular morbidity and cause-specific death.[17–21] In 2009, the ERFC agreed to extend analyses to anthropometric markers.[22] The current analyses focus on the 121 contributing prospective studies that, in addition to information on adult height at the initial (baseline) examination, also had information on age and sex at entry, did not select participants on the basis of having previous chronic disease (including vascular disease), recorded cause-specific mortality and/or vascular morbidity (i.e. non-fatal myocardial infarction or stroke) using clearly defined criteria, and accrued >1 year of follow-up. Study details are presented in Supplementary Table 1, available as Supplementary data at *IJE* online; acronyms are in the Supplementary Appendix, available as Supplementary data at *IJE* online. There were 1 085 949 participants who had no known history of vascular disease (i.e. myocardial infarction, angina or stroke, as defined in each study) at baseline. For 875 782 (81%) of the participants, height was measured using standardized protocols; for the remainder, height was self-reported (Supplementary Table 1, available as Supplementary data at *IJE* online). Overall, 619 984 participants had information on smoking status, blood pressure, history of diabetes, body mass index (BMI) and total cholesterol, and 585 084 participants had information on smoking status and socio-economic indicators. In registering fatal outcomes, all contributing studies used coding from the 'International Classification of Diseases' to at least three digits or study-specific classification systems, and ascertainment was based on death certificates. Attribution of death refers to the primary cause (or, in its absence, the underlying cause[23]) provided. Of the 121 contributing studies, 80 studies also involved medical records, autopsy findings and other supplementary sources to help classify deaths, 78 studies used standard definitions of myocardial infarction based on World Health Organization criteria and 59 studies reported diagnosis of strokes on the basis of typical clinical features and brain imaging and attributed stroke subtype.

Details of the statistical methods have been reported previously.[24] Height was normally distributed and the pooled within-study standard deviation (SD) was 6.5 cm for both males and females. Following the example of previous reports from the ERFC,[17–22] we assessed associations of height and fatal or first-ever non-fatal coronary disease or stroke and cause-specific mortality, including deaths from vascular disease, cancer and non-vascular conditions not attributed to cancer, as well as further subdivisions of these outcomes (e.g. site-specific cancers; see definitions in Supplementary Table 2, available as Supplementary data at *IJE* online). All participants contributed either the first non-fatal outcome or death during follow-up (i.e. deaths preceded by non-fatal coronary disease or stroke were not included in the main analyses), ignoring the few outcomes occurring before the age of 40 years. Subsidiary analysis was done for fatal outcomes without censoring of previous non-fatal outcomes. Analyses involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random-effects meta-analysis. Hazard ratios (HRs) were calculated using Cox proportional hazard regression models stratified by sex and decades of year of birth. The proportional hazard assumptions were satisfied. For each outcome, participants were censored if they were lost to follow-up, experienced another outcome or reached the study's end of follow-up. For the six contributing nested case–control studies within prospective cohorts, odds ratios were calculated using, where appropriate, conditional or unconditional logistic regression models, taking into account relevant matching factors.

To assess the shape of association, study- and sex-specific HRs calculated within quantiles of baseline height were pooled on a log scale by multivariate random-effects meta-analysis and plotted against mean height within each quantile. To reflect the amount of information within each group (including the reference group), 95% confidence intervals (CIs)

were estimated from variances attributed to the groups.[25] Since associations were approximately similar in both sexes (see Results section), further analyses were performed in males and females combined (parallel analyses were done in each sex separately). When associations were approximately log-linear, regression coefficients were calculated to estimate the HRs per 1 SD (i.e. 6.5 cm) greater baseline height. Unless specified otherwise, HRs were adjusted for age, sex, year of birth and smoking only (current smokers vs any other status). To explore potential biological pathways underlying associations, HRs were further adjusted for systolic blood pressure, history of diabetes, BMI, waist circumference, waist-to-hip ratio, total and high density lipoprotein cholesterol, triglyceride, C-reactive protein, fibrinogen, alcohol consumption or socio-economic indicators (i.e. educational attainment and occupational category). We investigated effect modification with formal tests of interaction, and calculated *P*-values for interaction with continuous variables, when appropriate. Diversity between studies was investigated by grouping studies with recorded characteristics and meta-regression. In the event of missing data, we conducted analyses in subsets of participants with complete information on relevant covariates. Evidence of heterogeneity was indicated by the I^2 statistic.[26] We corrected for regression dilution bias[27,28] using serial measurement in 355 391 participants from 67 cohorts, which used standardized protocols to measure height (mean interval: 5.5 years). We investigated small study effects. Analyses were carried out in Stata release 11. The study was approved by the Cambridgeshire Ethics Review Committee and analysed independently from its funders.

Results

Among the 1 085 949 participants included, the mean (±SD) age at baseline was 55±10 years; 48% were women (Table 1). Most participants were in Europe (60%) or North America (33%) (Supplementary Table 1, available as Supplementary data at *IJE* online). Median year of baseline survey was 1986 (interquartile range: 1976–92). Although mean height varied across studies, SDs were similar across studies (Supplementary Figure 1, available as Supplementary data at *IJE* online). Overall mean (SD) height was 173 ± 6.5 cm in men and 160 ± 6.5 cm in women. Height was negatively correlated with age at baseline, decreasing by an average of 0.7 cm every 5 years in adulthood (Figure 1A). In contrast, mean adulthood height adjusted to a given age (e.g. 50 years) among these people born between 1900 and 1960 increased across each decade of birth year by ~0.5–1 cm per decade (Figure 1B).

At baseline, there were modest and positive correlations of height with body weight, waist and hip circumference, but weakly negative correlations with blood pressure, lipids and inflammation biomarkers (Supplementary Table 3A and Supplementary Figure 2, available as Supplementary data at *IJE* online). On average, people of white European ancestry were 8.46 cm taller than East Asians, alcohol drinkers were 0.64 cm taller than non-drinkers, people without diabetes were 0.34 cm taller than those with diabetes, people with more education were 5.09 cm taller than others and people with office jobs were 1.55 cm taller than manual workers (Supplementary Table 3B, available as Supplementary data at *IJE* online). As would be expected for a trait that is stable in middle-aged people, the regression-dilution ratio for adult height, adjusted for age, sex and year of birth, was close to 1.0, i.e. 0.96 (95% CI: 0.95–0.97) during a mean interval of ~6 years. During 16.1 million person-years at risk (median 11.5 years to first outcome), there was a total of 174 374 deaths or major non-fatal vascular outcomes, comprising 19 768 non-fatal myocardial infarctions, 26 102 coronary deaths and 161 unspecified coronary heart disease events; 11 757 non-fatal and 9534 fatal strokes; 13 345 deaths from other vascular diseases, 49 722 deaths from cancer, 34 527 deaths from other causes and 9458 deaths of unknown or ill-defined cause. The overall association of height with death from any cause was weakly inverse and possibly curvilinear (Figure 2).

Height and cardiovascular diseases

There were continuous inverse associations between baseline height and risk of coronary disease and stroke across the range of values, with possible attenuation at higher values (Figure 2 and Supplementary Figure 3, available as Supplementary data at *IJE* online). Associations of baseline height with vascular outcomes are shown in Figure 3. After adjustment for age, sex, smoking and birth year, HRs per 1 SD higher baseline height were 0.93 (0.91–0.94) for coronary disease, 0.94 (0.90–0.97) for ischaemic stroke, 0.90 (0.85–0.95) for haemorrhagic stroke, 0.91 (0.84–0.98) for subarachnoid haemorrhage, 0.95 (0.92–0.98) for unclassified stroke and 0.94 (0.89–0.99) for death from heart failure. In contrast, the corresponding HRs were 1.12 (1.03–1.21) for pulmonary embolism and 1.12 (1.05–1.20) for ruptured aortic aneurysm (Figure 3). HRs were not appreciably altered after additional adjustment for blood pressure, history of diabetes, lipids, C-reactive protein, fibrinogen, BMI, waist circumference, waist-to-hip ratio, alcohol consumption or indicators of socioeconomic status (Tables 2 and 3). HRs for coronary disease and stroke appeared to become more extreme with later decade of birth, but HRs did not vary materially by age, sex, mean height levels or other characteristics recorded (Supplementary Figures 4 and 5, available as Supplementary data at *IJE* online). Heterogeneity in HRs for height was only partly explained by the

Table 1 Baseline data used in the current analysis

Characteristics	No. of studies	No. of participants	Mean (SD) or %
Height (cm)	121	1 085 949	173 (6.5)/160 (6.5)[a]
Demographic factors			
Age at survey (years)	121	1 085 949	55 (10)
Sex	121	1 085 949	
Female		522 257	48%
Male		563 692	52%
Ethnicity	93	549 459	
East Asian		39 800	7%
Black		29 895	5%
Other		11 369	2%
White		468 395	85%
Physical measurements			
BMI (kg/m^2)	121	1 081 839	26.0 (4.1)
Systolic blood pressure (mmHg)	117	840 352	136 (19)
History of diabetes	110	833 766	
Yes		39 106	5%
No		794 660	95%
Lipid markers			
Total cholesterol (mmol/l)	117	824 332	5.84 (1.13)
Non-HDL cholesterol (mmol/l)	100	452 696	4.48 (1.11)
HDL cholesterol (mmol/l)	100	453 106	1.34 (0.37)
Log_e triglyceride (mmol/l)	99	661 385	0.33 (0.52)
Inflammation biomarkers			
Log_e CRP (mg/l)	49	138 177	0.64 (1.10)
Fibrinogen (μmol/l)	46	201 724	9.28 (2.15)
Lifestyle and socio-economic factors			
Smoking status	120	1 010 302	
Current		315 789	31%
Not current		694 513	69%
Alcohol status	92	511 895	
Current		325 781	64%
Not current		186 114	36%
Level of education reached	61	374 737	
Tertiary		106 396	28%
Secondary		187 779	50%
Primary		66 758	18%
No schooling		13 804	4%
Occupation or job	59	360 531	
Office		127 181	35%
Not working		90 013	25%
Other		47 468	13%
Manual		95 869	27%

[a]Mean (SD) height in males/mean (SD) height in females.
BMI, body mass index; SD, standard deviation; HDL, high density lipoprotein; CRP, C-reactive protein.

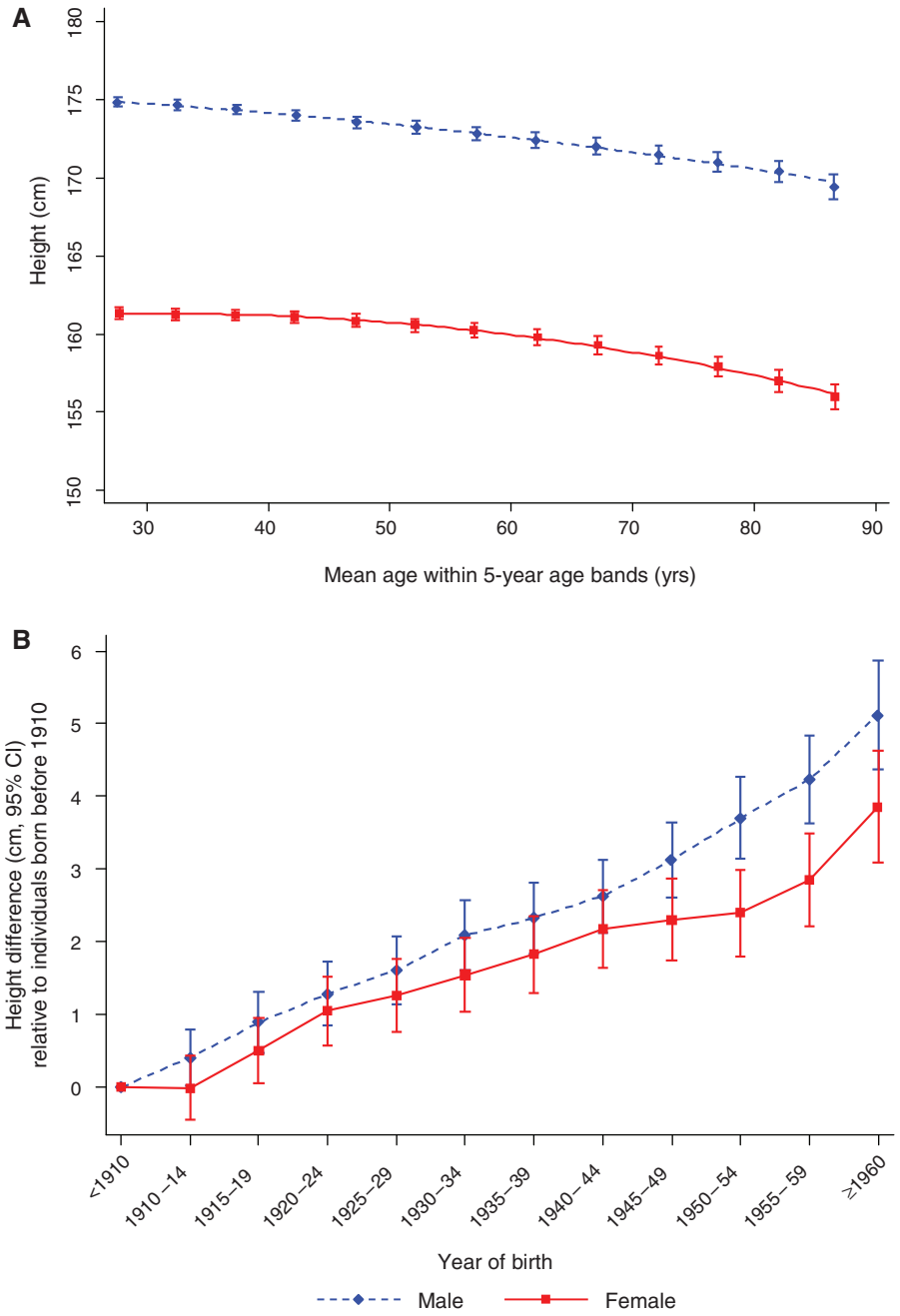

Figure 1 Mean baseline height within 5-year age bands adjusted for calendar year (A) and differences in baseline height adjusted to age 50 years across calendar years relative to individuals born before 1910 (B). All analyses were adjusted for between-study differences in mean height via inclusion of a random intercept term in the multilevel mixed effects model. Error bars represent the 95% CI

characteristics recorded (Supplementary Figures 4 and 5, available as Supplementary data at *IJE* online).

Height and cancer mortality and non-vascular non-cancer mortality

Height was positively and continuously associated with total cancer mortality (Figure 2 and Supplementary Figure 6, available as Supplementary data at *IJE* online). As regards site-specific cancers, height was negatively associated with death from oral and stomach cancers and was positively associated with death from melanoma and cancers of the pancreas, endocrine and nervous systems, breast, ovary, prostate, colorectum, blood and lung (Figure 4). HRs for breast cancer mortality were similar

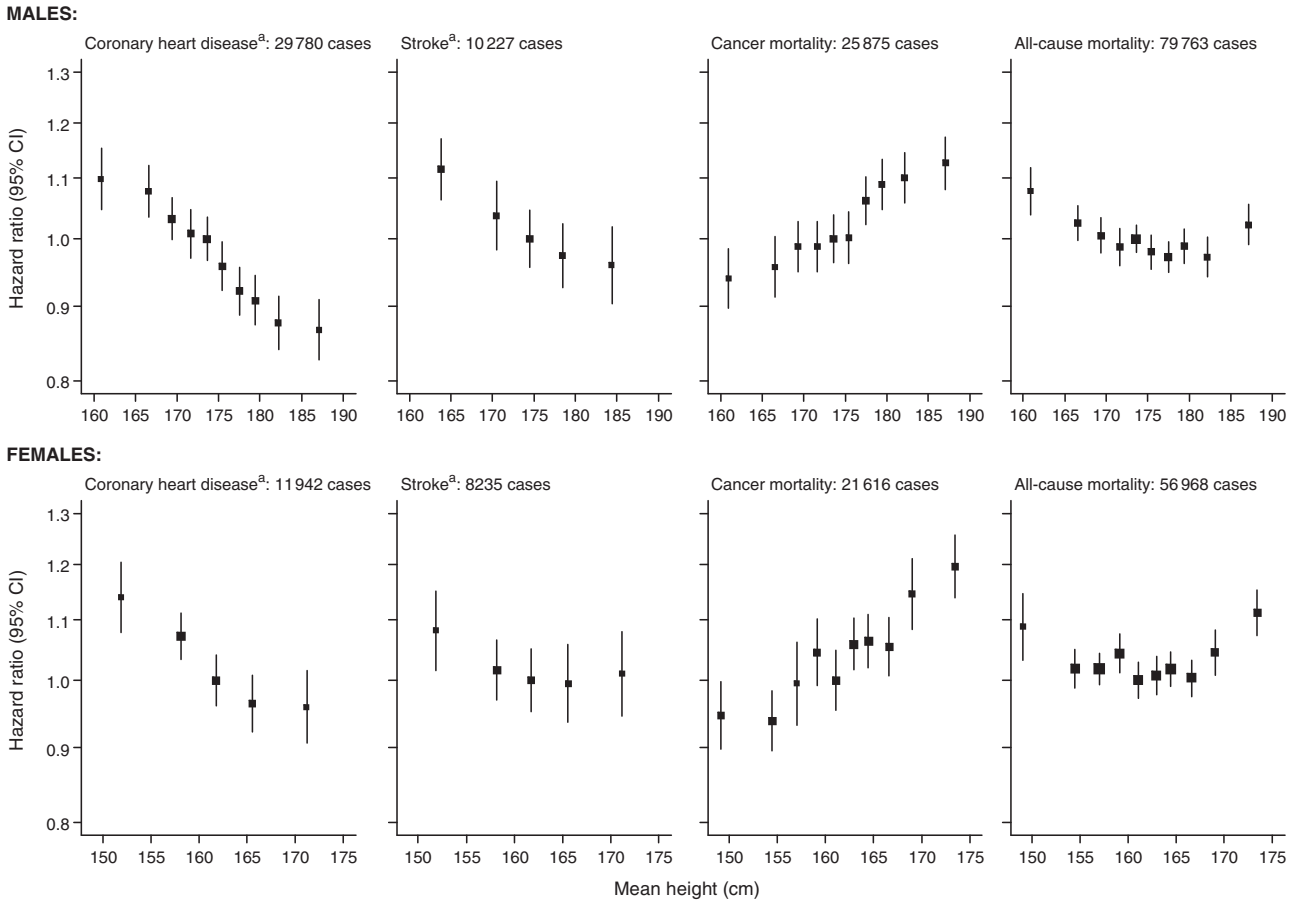

Figure 2 HRs for coronary heart disease, stroke, cancer mortality and all-cause mortality across quantiles of baseline height values, among males and females. [a]Includes both fatal and non-fatal events. Adjusted study-specific $\log_e$ HRs were combined by multivariate random-effects meta-analysis. Regression analyses were adjusted for age at baseline and smoking status (current smokers vs any other status), and stratified by decades of year of birth (<1920, 1920–29, 1930–39, 1940–49, 1950–59, ⩾1960) and, where appropriate, by trial arm. Studies with <5 events of an outcome for each sex were excluded from the analysis of that particular outcome. Sizes of the data markers are proportional to the inverse of the variance of the $\log_e$ HRs. Reference groups are the fifth decile or third quintile in each plot

across age-at-risk groups (Supplementary Figure 7, available as Supplementary data at *IJE* online). Adjustment for several risk factors for chronic disease did not appreciably alter HRs for cancer death (Tables 2 and 3). There were no clear associations of height with death from cancer of the liver, connective tissue, oesophagus or bladder. For every 6.5 cm greater height, HRs were 0.84 (0.80–0.89) for death from chronic obstructive pulmonary disease, 0.89 (0.83–0.96) for death from mental disorders, 0.89 (0.84–0.93) for death from liver disease, 0.96 (0.92–1.00) for death from external causes and 0.96 (0.92–1.00) for death from pneumonia (Figure 4 and Supplementary Figure 8, available as Supplementary data at *IJE* online).

Similar results to those reported here were observed in a range of subsidiary analyses such as those that restricted attention to participants with measured (rather than self-reported) height (available on request); omitted the initial 5-years of follow-up, current smokers, participants of non-European descent or with a history of diabetes (Table 3); used fixed effect models (Supplementary Figure 9, available as Supplementary data at *IJE* online) or sex-specific models (Table 3); used age (rather than time-on-study) as timescale in regression models (Table 3); included fatal outcomes without censoring previous non-fatal outcomes (Supplementary Table 4, available as Supplementary data at *IJE* online) or corrected concurrently for regression dilution in height and in potential confounders and mediators (Supplementary Table 5, available as Supplementary data at *IJE* online). There was no evidence of small study effects (Supplementary Figure 10, available as Supplementary data at *IJE* online). In an exploratory between-study (ecological) analysis, there were no clear associations between study-level mean height values and age-adjusted incidence rates for coronary heart disease, stroke or cancer mortality (Supplementary Figure 11, available as Supplementary data at *IJE* online).

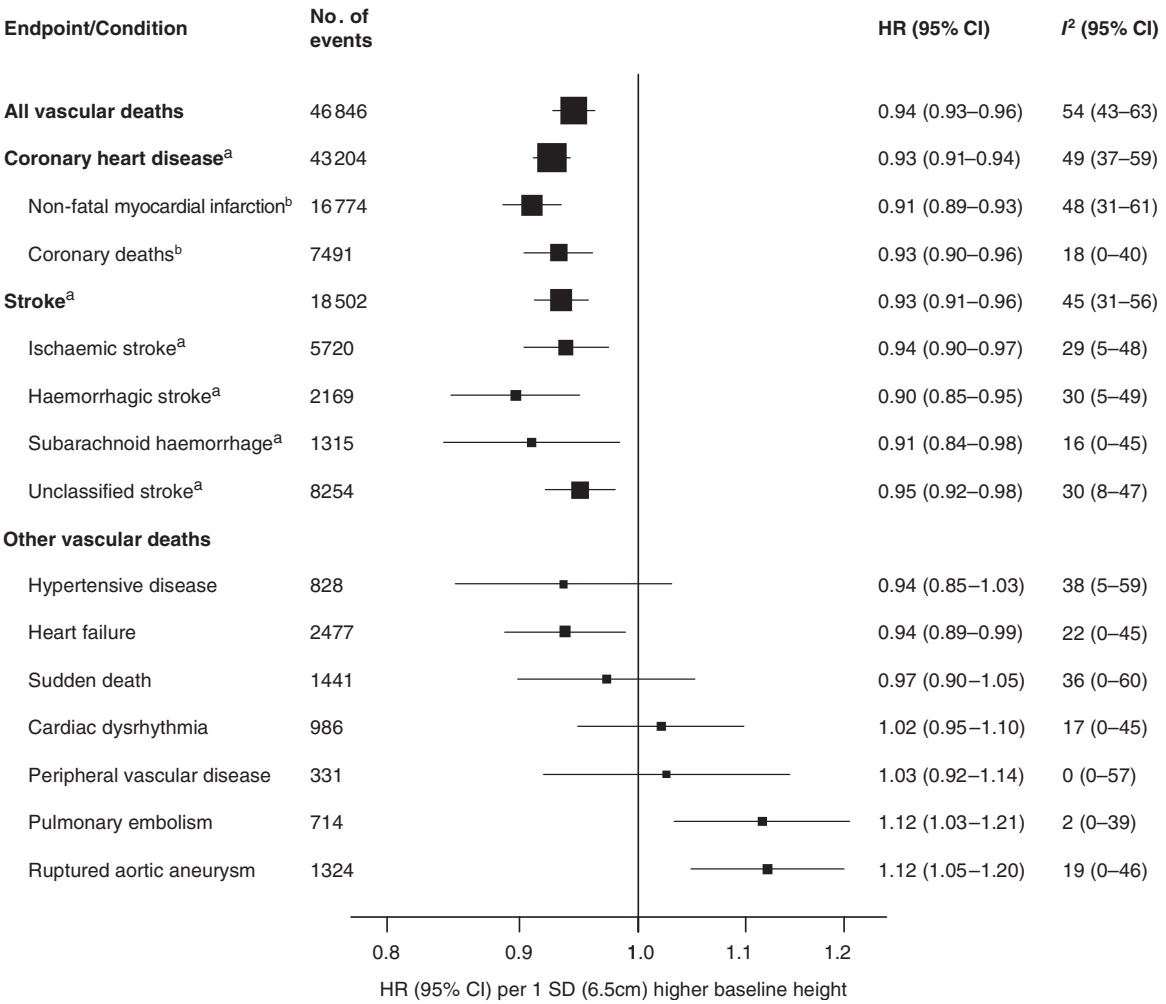

Figure 3 HRs for vascular outcomes per 1 SD (6.5 cm) higher baseline height, adjusted for age, sex, smoking and year of birth. [a]Includes both fatal and non-fatal events. [b]Restricted to studies contributing to both outcomes. Causes of other vascular deaths are ordered by their strength of association. HRs were adjusted for age at baseline and smoking status (current smokers vs any other status), and stratified by decades of year of birth (<1920, 1920–29, 1930–39, 1940–49, 1950–59, ⩾1960) and, where appropriate, by sex and trial arm. Studies with <5 events were excluded from the analysis of that particular outcome. For comparison with previous publications, HRs per 5 cm higher baseline height were 0.96 (0.94–0.97) for all vascular deaths; 0.94 (0.93–0.96) for coronary heart disease and 0.95 (0.93–0.97) for stroke

Discussion

Our results have demonstrated that, although the risk of all-cause mortality is 3% lower per 6.5 cm greater height, disaggregation by cause-specific mortality reveals stronger and directionally opposing relationships with risk of death from several different major causes of chronic disease. HRs per 6.5 cm greater height ranged from 1.26 (1.12–1.42) for risk of death from melanoma to 0.84 (0.80–0.89) for risk of death from chronic obstructive pulmonary disease. Because the disease associations of height observed here were not appreciably altered after adjustment for long-term smoking, adiposity, inflammation biomarkers, blood pressure, lipids and diabetes, it reduces the likelihood that these factors are mediators of the associations in this study. Hence, the results of our study suggest that variations in adult height (and, by implication, the genetic and other determinants of height) have pleiotropic effects on several major adult-onset diseases. Furthermore, the current data demonstrate that mean adult height in developed countries has increased by 0.5-1 cm per decade for those born between 1900 and 1960. Hence, although height is 80–90% heritable,[29,30] the increases in height noted over recent decades have almost certainly been due to non-genetic factors.

The current results primarily have implications for understanding disease aetiology rather than for clinical risk prediction. Taller people have a lower risk of death from coronary disease, stroke subtypes, heart failure, oral and gastric cancers, chronic obstructive

Table 2 HRs for coronary heart disease, stroke and cancer mortality per 1 SD (6.5 cm) higher baseline height, adjusted for baseline levels of biological, socio-economic and behavioural risk factors

	Coronary heart disease[a]			Stroke[a]			Cancer mortality		
	No. of participants	No. of events	HR (95% CI)	No. of participants	No. of events	HR (95% CI)	No. of participants	No. of deaths	HR (95% CI)
Progressive adjustment									
Age, sex and year of birth	615 842	30 893	0.92 (0.90–0.94)	600 605	12 726	0.92 (0.90–0.95)	548 327	25 195	1.04 (1.02–1.06)
Plus smoking status	615 842	30 893	0.92 (0.91–0.94)	600 605	12 726	0.92 (0.90–0.95)	548 327	25 195	1.05 (1.03–1.06)
Plus systolic blood pressure	615 842	30 893	0.93 (0.91–0.95)	600 605	12 726	0.94 (0.91–0.96)	548 327	25 195	1.05 (1.03–1.06)
Plus history of diabetes	615 842	30 893	0.93 (0.91–0.95)	600 605	12 726	0.94 (0.91–0.96)	548 327	25 195	1.05 (1.03–1.06)
Plus BMI	615 842	30 893	0.94 (0.92–0.96)	600 605	12 726	0.94 (0.91–0.96)	548 327	25 195	1.05 (1.03–1.07)
Plus total cholesterol	615 842	30 893	0.95 (0.93–0.97)	600 605	12 726	0.94 (0.91–0.96)	548 327	25 195	1.05 (1.03–1.06)
Additional adjustment									
Lipid markers									
Basic model[b]	315 881	13 448	0.95 (0.94–0.97)	304 657	7295	0.95 (0.92–0.98)	–	–	–
Plus non-HDL-C, HDL-C and $\log_e$ triglyceride[c]	315 881	13 448	0.95 (0.93–0.97)	304 657	7295	0.95 (0.92–0.98)	–	–	–
Inflammation biomarkers									
Basic model[b]	126 314	8473	0.93 (0.91–0.95)	117 054	3659	0.98 (0.94–1.03)	97 634	4483	1.05 (1.01–1.09)
Plus $\log_e$ CRP	126 314	8473	0.94 (0.91–0.96)	117 054	3659	0.99 (0.94–1.03)	97 634	4483	1.05 (1.01–1.10)
Basic model[b]	179 250	8020	0.94 (0.91–0.97)	171 161	4392	0.95 (0.91–1.00)	166 313	6226	1.04 (1.01–1.07)
Plus fibrinogen	179 250	8020	0.95 (0.92–0.97)	171 161	4392	0.96 (0.92–1.00)	166 313	6226	1.04 (1.01–1.07)
Lifestyle and socio-economic factors									
Age, sex, smoking and year of birth	362 636	20 833	0.93 (0.91–0.95)	352 052	8623	0.95 (0.92–0.98)	322 527	15 172	1.05 (1.02–1.07)
Plus education	362 636	20 833	0.94 (0.92–0.96)	352 052	8623	0.96 (0.93–0.99)	322 527	15 172	1.06 (1.03–1.09)
Age, sex, smoking and year of birth	357 759	15 892	0.93 (0.91–0.95)	350 935	7373	0.94 (0.91–0.96)	343 381	12 445	1.03 (1.01–1.05)
Plus occupation or job	357 759	15 892	0.93 (0.91–0.96)	350 935	7373	0.94 (0.92–0.97)	343 381	12 445	1.04 (1.02–1.06)
Age, sex, smoking and year of birth	500 367	22 003	0.92 (0.90–0.93)	488 113	11 076	0.93 (0.91–0.95)	468 497	17 353	1.03 (1.01–1.05)
Plus alcohol consumption	500 367	22 003	0.92 (0.90–0.93)	488 113	11 076	0.93 (0.91–0.96)	468 497	17 353	1.03 (1.01–1.05)

[a]Includes both fatal and non-fatal events.
[b]All basic models were adjusted for age, sex, smoking status (current smokers vs any other status), year of birth, systolic blood pressure, history of diabetes, BMI and total cholesterol.
[c]Total cholesterol was not included in further adjustments.
HRs are presented per 1 SD (6.5 cm) higher baseline height. HRs were adjusted as shown, and stratified by decades of year of birth (<1920, 1920–29, 1930–39, 1940–49, 1950–59, ⩾1960), and, where appropriate, by sex and trial arm. Analyses were restricted to subsets with complete information. Studies with <5 events were excluded from the analysis of that particular outcome.
HDL-C, high density lipoprotein cholesterol; CRP, C-reactive protein.

Table 3 HRs for major outcomes per 1 SD (6.5 cm) higher baseline height, adjusted for age, sex, year of birth and smoking status

Description of supplementary analysis	Outcome	No. of events	HR (95% CI)	I^2 (95% CI)
Excluding first 5 years of follow-up	Coronary heart disease[a]	31 680	0.93 (0.91–0.95)	44 (29–56)
	Stroke[a]	13 590	0.93 (0.91–0.96)	47 (32–59)
	Cancer mortality	39 346	1.05 (1.04–1.07)	18 (0–38)
Excluding current smokers	Coronary heart disease[a]	27 290	0.92 (0.90–0.94)	45 (31–56)
	Stroke[a]	14 182	0.94 (0.92–0.97)	40 (24–53)
	Cancer mortality	29 029	1.04 (1.03–1.06)	11 (0–31)
	Lung	3164	1.07 (1.03–1.10)	0 (0–30)
	Respiratory disease	5435	0.93 (0.88–0.98)	54 (40–65)
Excluding people with a history of diabetes	Coronary heart disease[a]	40 743	0.92 (0.91–0.94)	44 (29–55)
	Stroke[a]	16 197	0.94 (0.91–0.96)	43 (28–55)
	Cancer mortality	45 089	1.04 (1.03–1.06)	19 (0–38)
Analysis with age (rather than time-on-study) as timescale	Coronary heart disease[a]	43 204	0.92 (0.91–0.94)	52 (40–61)
	Stroke[a]	18 502	0.93 (0.91–0.95)	46 (32–57)
	Cancer mortality	47 502	1.04 (1.03–1.06)	22 (0–39)
Excluding non-European descents	Coronary heart disease[a]	40 743	0.92 (0.91–0.94)	44 (29–55)
	Stroke[a]	16 197	0.94 (0.91–0.96)	43 (28–55)
	Cancer mortality	45 089	1.04 (1.03–1.06)	19 (0–38)
Restricted to men only	Coronary heart disease[a]	30 958	0.93 (0.91–0.94)	39 (23–51)
	Stroke[a]	10 227	0.93 (0.90–0.95)	34 (16–48)
	Cancer mortality	25 875	1.04 (1.03–1.06)	4 (0–26)
	All-cause mortality	79 763	0.97 (0.96–0.98)	56 (45–64)
Restricted to women only	Coronary heart disease[a]	12 236	0.93 (0.90–0.95)	29 (5–46)
	Stroke[a]	8235	0.94 (0.91–0.98)	43 (24–57)
	Cancer mortality	21 616	1.05 (1.02–1.07)	17 (0–39)
	All-cause mortality	56 968	0.97 (0.95–0.99)	59 (48–68)
Adjustment for waist circumference instead of BMI[b]	Coronary heart disease[a]	6043	0.93 (0.90–0.96)	14 (0–41)
	Stroke[a]	4016	0.95 (0.91–1.00)	32 (0–54)
	Cancer mortality	4950	1.04 (1.00–1.08)	28 (0–52)
Adjustment for waist-to-hip ratio instead of BMI[b]	Coronary heart disease[a]	5913	0.95 (0.92–0.98)	5 (0–33)
	Stroke[a]	3908	0.97 (0.92–1.02)	37 (5–58)
	Cancer mortality	4840	1.05 (1.00–1.09)	30 (0–53)

[a]Includes both fatal and non-fatal events.
[b]Analyses additionally adjusted for systolic blood pressure, history of diabetes and total cholesterol.
HRs are presented per 1 SD (6.5 cm) higher baseline height. HRs were adjusted for age at baseline and smoking status (current smokers vs any other status), and stratified by decades of year of birth (<1920, 1920–29, 1930–39, 1940–49, 1950–59, ⩾1960), and, where appropriate, by sex and trial arm. Studies with <5 events were excluded from the analysis of that particular outcome.

pulmonary disease, mental disorders, liver diseases and external causes. Some of these conditions have previously been associated with height.[5,31–34] The inverse association between height and coronary disease has been proposed to be because of taller people having larger coronary vessel diameters, elevated insulin-like growth factors, slower heart rate and/or greater lung capacity.[5,15,35,36] Conflicting evidence exists regarding the magnitude of the association between adult height and risk of major stroke subtypes.[5] Whereas some studies have reported that associations of height with haemorrhagic stroke and ischaemic stroke are of similar magnitude to each other,[37–39] the current more powerful analysis (as well as some previous prospective studies[12,40,41]) reported slightly stronger associations with haemorrhagic stroke than ischaemic stroke. The explanation for this difference is not clear, but, since shorter adult height is believed to reflect, at least in part, poor nutrition and/or lower socio-economic circumstances in childhood, it suggests that haemorrhagic stroke may be more liable to such determinants than

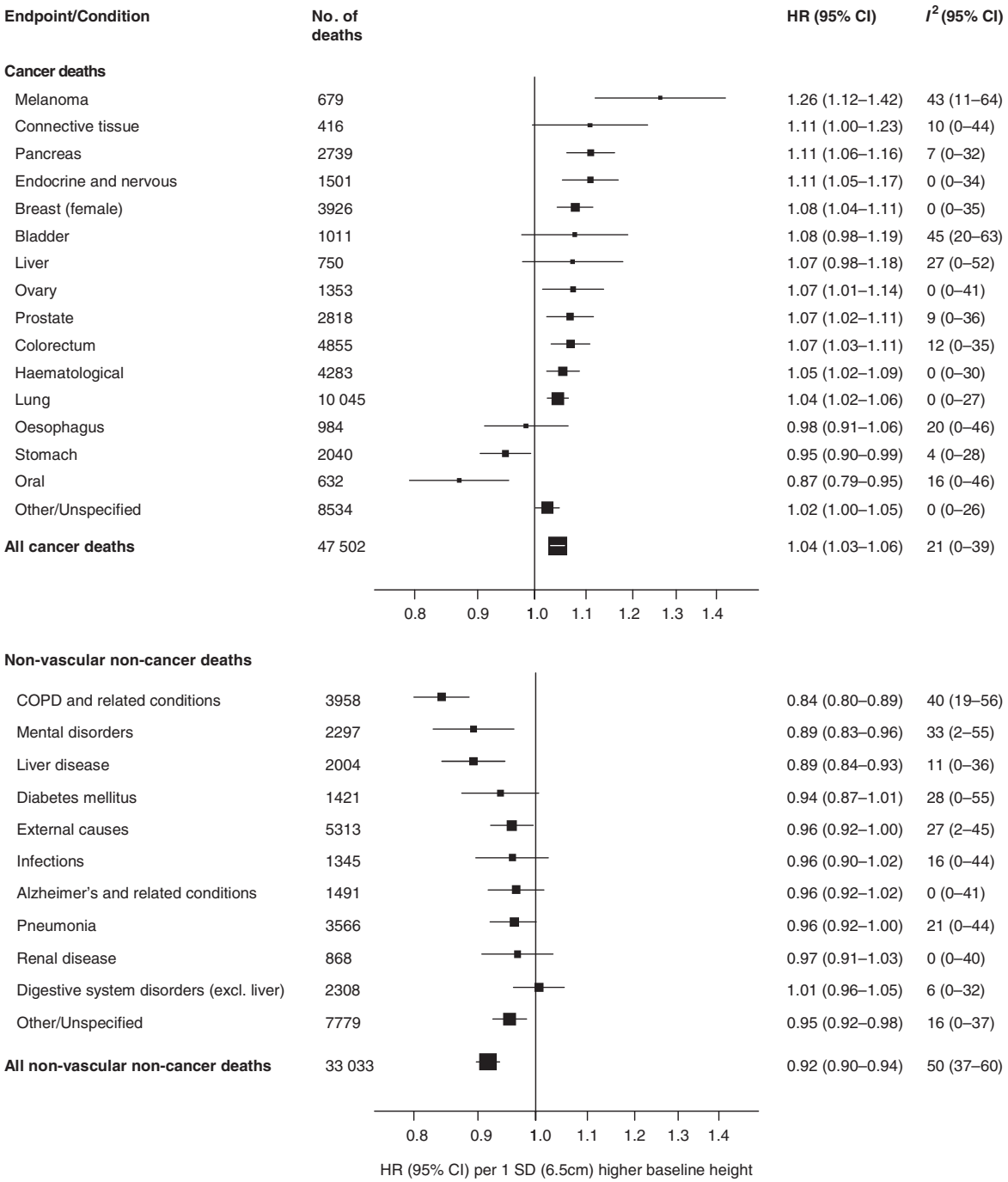

Figure 4 HRs for cause-specific non-vascular mortality per 1 SD (6.5 cm) higher baseline height, adjusted for age, sex, smoking and year of birth. With the exception of the classifications 'Other/Unspecified', causes of deaths are ordered by their strength of association. HRs were adjusted for age at baseline and smoking status (current smokers vs any other status), and stratified by decades of year of birth (<1920, 1920–29, 1930–39, 1940–49, 1950–59, ⩾1960) and, where appropriate, by sex and trial arm. Studies with <5 events were excluded from the analysis of that particular outcome. HR for all-cause mortality per 1 SD (6.5 cm) height was 0.97 (0.96–0.99), $I^2 = 69\%$ (63–75%) and for unknown or ill-defined cause was 0.96 (0.93–1.00), $I^2 = 45\%$ (27–58%). For comparison with previous publications, HRs per 5 cm higher baseline height were 1.03 (1.02–1.04) for all cancer deaths and 0.94 (0.92–0.95) for all non-cancer non-vascular deaths

ischaemic stroke.[33,34,42] In contrast, there were positive associations between adult height and risk of death from pulmonary embolism, which could be because of greater propensity to venous thrombosis owing to greater venous surface area or more venous valves in taller people,[43] and ruptured aortic aneurysm, which could be because of longer arteries being more prone to rupture.[44]

The current study has confirmed that taller people are at greater risk of death from several organ-specific malignancies such as melanoma, cancers of the pancreas, breast, ovary, prostate and colorectum.[6–9] We observed a HR of 1.04 for all cancer mortality per 6.5 cm greater height, which was similar to that reported in previous prospective studies.[6,9,45] It has been proposed that because taller people have larger organs, they have greater numbers of cells at risk of malignant transformation and/or proliferation.[46] For breast and other hormone-related cancers, it has been proposed that taller people have tumour-inducing hormonal and biochemical alterations[5,47] and/or genes linked with both skeletal growth and cancer risk.[48] The negative association we observed between height and death from gastric cancer is consistent with the known relevance to this malignancy of *Helicobacter pylori* infection, acquisition of which is related to poorer socio-economic circumstances in childhood.[15,49]

Our study of over 1 million adults was powerful, involved individual participant data, adjusted for several major risk factors, assessed risk factors serially in 355 000 participants and studied a wide range of common and less common disease outcomes in a standardized manner. Since we analysed only prospective cohort studies, we minimized potential biases. The generalizability of our findings is supported by broadly consistent results across 121 prospective cohorts in 24 countries. Due to the wide age ranges and periods of recruitment of the participants in our study, we were able to quantify the trend toward increasing height in successive birth cohorts. Nonetheless, residual bias could persist owing to unmeasured or imprecisely measured confounding factors (e.g. dietary factors and socio-economic factors, respectively). Height loss in adulthood may be related to development of co-morbidities, which could generate an association between height and mortality through reverse causation. However, sensitivity analyses, excluding the initial years of the follow-up period or restricting participants to young ages in which height loss is less likely to happen, suggest that potential bias owing to shrinkage was unlikely to change the HRs substantially. Apart from for coronary disease and stroke, we studied only fatal outcomes. Future studies will seek to investigate whether height-related genetic loci[4] are associated with the height-related diseases identified in this report, and to determine whether ethnic or geographical variation in genetic make-up could explain the current results. However, the scope for the latter explanation has been reduced because >90% of the participants in this study were of white European descent. The current study encourages more detailed investigation of specific early-life exposures[5] in relation to adult-onset diseases, encompassing risk factors from intra-uterine development, infancy, childhood and adolescence.

Conclusion

Adult height, which is an indicator of the interplay of genetic and early-life factors, has directionally opposing relationships with risk of death from several different major causes of chronic disease.

Supplementary Data

Supplementary Data are available at *IJE* online.

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KEY MESSAGES

- We analysed individual data on >1 million adults in whom 174 000 relevant deaths or events were recorded during 16 million person-years at risk.
- We found that whereas adult height is inversely related to risk of death from coronary disease, stroke subtypes, heart failure, stomach and oral cancers, chronic obstructive pulmonary disease, mental disorders, liver diseases and external causes, adult height is positively associated with risk of death from pulmonary embolism, ruptured aortic aneurysm and several organ-specific malignancies, such as melanoma and cancers of the pancreas, breast, ovary, prostate and colorectum.

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