Short stature is an independent risk marker for mortality and incident coronary heart disease only in women: a structural relationship?

Kısa boy mortalite ve insidan koroner kalp hastalığı riskinin yalnızca kadınlarda bağımsız bir belirtecidir: Yapısal ilişki mi?

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ABSTRACT

Objective: We evaluated the associations of short stature with coronary heart disease (CHD) risk or overall mortality, which vary with sex and ethnicity/race.
Methods: Such associations were studied prospectively at a mean 13.5-years' follow-up in a population-based sample of 3394 Turkish adults (mean age 44±11 years) using Cox proportional hazards models. Covariates of height were sought in sex-specific tertiles.
Results: Height averaged 162.7±6.5 cm. Age-adjusted estimated marginal means for serum triglycerides, C-reactive protein and complement C3 in women (but not men) were significantly higher with decreasing height tertiles. In sex- and age-adjusted models, height was associated in men with neither incident CHD, nor death. In women, 1-SD increment (6.5 cm) in height only tended to marginal inverse association with CHD, but predicted significantly all-cause death (HR 0.83, 95% CI 0.59-0.98); HR attenuated only marginally after further adjustment for family income bracket, smoking status, alcohol usage, systolic blood pressure, serum high-density lipoprotein (HDL)- and non HDL-cholesterol. A threshold below 160 cm of female height doubled the adjusted risk of death compared to taller women.
Conclusion: In contrast to men, short stature in Turkish women tends to be an independent risk marker for CHD, and height below 160 cm is a strong marker of death. Gender-specific early-life influences enhancing pro-inflammatory state may affect death and future CHD.
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Key words: Body height, coronary heart disease, epidemiology, gender difference, mortality, risk factors, regression analysis

ÖZET

Amaç: Bireyin boyunun koroner kalp hastalığı (KKH) riski ve mortalite ile ilişkisi, cinsiyete ve etnisite/ırka göre değişir. Anılan ilişkiler, popülasyona dayalı bir Türk yetişkin örnekleminde incelendi.
Yöntemler: Başlangıçta ortalama 44±11 yaşındaki 3394 yetişkin ortalama 13.5 yıllık izlemede Cox orantılı hazard modelleri kullanılarak incelendi. Boyun kovaryatları cinsiyete özgü üçte birlik dilimlerde araştırıldı.
Bulgular: Ortalama boy erkekte 169.5±6.6 cm, kadında 156.0±6.4 cm idi. Yaş ayarlı serum trigliseridleri, C-reaktif protein ve kompleman C3 (erkekte değil ama) kadında azalan boy dilimlerinde anlamlı olarak yüksek bulundu. Cinsiyet ve yaş ayarlı modellerde boy erkekte ne insidan KKH, ne de ölümle ilişkiliydi. Kadında ise, boyda 1 standart sapmalık (6.5 cm) artış KKH ile marjinal biçimde ters ilişki gösterirken, toplam ölüm oranını anlamlı olarak öngördü: hazard oranı (HR) -0.83 (%95GA 0.59-0.98). Ek olarak aile gelir dilimi, sigara içiciliği, alkol kullanımı, sistolik kan basıncı, serum yüksek-yoğunluklu lipoprotein (HDL)- ve HDL dışı- kolesterol için ayarlanınca, HR ancak marjinal biçimde zayıfladı. Kadında boyun 160 cm'den kısa olması, daha uzun olanlara kıyasla, ölüm oranını ikiye katlıyordu.
Sonuç: Erkekten farklı olarak, Türk kadınında kısa boy KKH için bağımsız bir risk belirteci eğilimi sergilerken, 160 cm'den kısa boy ölüm için güçlü bir belirteçtir. Hayatın erken dönemlerinde yangı durumunu arttıran cinsiyete özgü etkiler ölüm ve gelecekteki KKH riskini etkileyebilir.
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Anahtar kelimeler: Vücut boyu, koroner kalp hastalığı, epidemiyoloji, cinsiyet farkı, mortalite, risk faktörleri, regresyon analizi

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Introduction

Short stature is recognized to be inversely associated with risk of coronary heart disease (CHD) (1-3), or its mortality (4, 5); yet exceptions exist (6-8). Relationship of all-cause mortality has been reported in fewer large prospective studies (4). The Renfrew/Paisley study demonstrated a weak inverse association with overall mortality, which was higher in women than men (4) and corresponded in magnitude to multivariable-adjusted relative risks of 0.91 to 0.94 per increment of 1-standard deviation (SD). Such associations may be generated by genetic, socioeconomic or environmental factors. Noteworthy is that gender is a major effect modifier (9-11), and the stated associations do not appear to hold generally as strongly in females in whom the ratio of developing CHD and cancer diverges from males (12). Race or ethnicity is a second modulator: Large differences exist in CHD incidence between populations, and shorter populations have lower CHD risk compared with the taller ones (13). Most of the available studies have been largely on Caucasian populations, some also on East Asian populations in whom the inverse association with CHD seems to be much weaker or lacking (12, 14). Except for one study on Israeli male civil servants (7) in whom a relation between height and CHD was notably not observed, data on this link in Middle-Eastern populations are lacking and added information is needed.

Moreover, interactions between height and other major risk factors for CHD still remain unknown. In over 10.000 older Chinese men and women, height (especially sitting height) was associated significantly though modestly with lower pulse pressure, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol and higher triglycerides (and a tendency to higher glucose and diabetes likelihood) (15). Socioeconomic factors during childhood and environmental factors related to early nutrition influencing fetal growth may be underlying this link, but genetic factors may also play a role in the "early programming" of disease (16, 17).

The aim of this study was to investigate 1) body height's possible link to cardiovascular risk factors, 2) its association with overall mortality and 3) with CHD incidence, after adjusting for a wide range of risk factors in Turkish adults who represent both a shorter population than Western people and have a high prevalence of the metabolic syndrome (MetS) (18).

Methods

Population sample

The Turkish Adult Risk Factor (TARF) study is a longitudinal population-based cohort study on cardiac disease and its risk factors in adults in Turkey, carried out biennially in 59 communities in all geographical regions (19). It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural-urban distribution (19). Its cohort was recruited initially in 1990, followed by enrollments in the 1997/98 and 2002/03 surveys which together made up one-third of the original cohort. These periods formed the baseline. Participants, 20 and 28 years of age or older at baseline, were examined periodically up to the survey 2009/10. Individuals with no follow-up were excluded, and the remaining 3394 participants formed the cohort of the current study. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Participants gave written consent for participation. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12-lead electrocardiogram.

Measurements of risk variables

Weight and height were measured at examination without shoes. Blood pressure (BP) was measured while seated, using the right arm, with a sphygmomanometer (Erka, Bad Tölz, Germany). The mean of two recordings taken at least 3 min apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Self-reported cigarette smoking was categorized into never-smokers, former smokers (having stopped for at least 3 months prior to the study) and smokers (regularly one or more cigarettes daily). Participants categorized themselves at baseline into five predefined increasing family income brackets.

Plasma concentrations of total and HDL cholesterol, fasting triglycerides and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. Low-density lipoprotein (LDL)-cholesterol values were calculated according to the Friedewald formula. In the final five examinations, the previously measured parameters, as well as insulin and C-reactive protein (CRP) values were assayed in a single central laboratory. Blood samples were shipped to Istanbul to be stored at -75°C, until analyzed. Serum concentrations of apo A-I and B, complement C3c (C3) and CRP was measured by the Behring nephelometry (Behring Diagnostics, Marburg, Germany). Fibrinogen levels were assayed in plasma latest within two hours after blood was collected in sodium citrate containing vacutainers, by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit. External quality control was performed with a reference laboratory in a random selection of 5-6% of participants. Data on baseline triglycerides, CRP, fibrinogen and C3 were available in 71%, 79%, 65% and 40% of participants, respectively.

Definitions and outcomes

Diagnosis of non-fatal CHD was based on the presence of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardıogram (ECG) (20), or on a history of myocardial revascularization. Typical angina and, in women, age >45 years were prerequisite

for a diagnosis when angina was isolated. ECG changes of ''ischemic type'' of greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarction sequel or myocardial ischemia, respectively. Cause of death was assigned in accordance with the information on the mode of death obtained from first-degree relatives and/or local health personnel, considering also pre-existing clinical and laboratory findings elicited during biennial examinations.

Statistical analysis

Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, Ill., Nr. 9026510). Results are shown as mean±standard deviation (SD), as percentages, and as estimated marginal mean±standard error (SE). Due to skewed distribution, values derived from log-transformed (geometric) means were used for serum CRP. Two- sided t-tests and Pearson's Chi-square tests were used to analyze the differences between means and proportions of two groups. ANOVA was used to detect differences between means of multiple groups, followed by pairwise comparisons with Tukey HSD tests; pairwise comparisons with Bonferroni adjustments were made to detect significance between groups of estimated means. For tertile analyses, the intermediate tertiles were formed by 167 to 172 cm in men and 153 to 159 cm in women, ≥173 cm and ≥160 cm making up the tall tertiles, respectively. Various covariates of height tertiles were sought with the purpose of examining possible non-linear associations. To present baseline characteristics, participants were dichotomized for height using ≤170 and ≤156 cm in men and women, respectively (forming 58.6% and 54.2% of the sample).

In predicting outcomes from baseline examination in multivariate analyses, estimates (and 95% confidence intervals) for hazard ratios (HR) were obtained by use of Cox proportional hazards regression analyses, in which the estimated dates of death and onset of CHD recorded during periodical follow-up were used. Proportionality was upheld between the independent variables and follow-up time. Such models were adjusted for variables. Analyses by height tertiles were also performed. HRs were expressed in terms of 1-SD increment which was 3-fold for the log-transformed CRP. A value of $p<0.05$ on the two-sided test was considered statistically significant.

Results

The study sample was formed by 3394 participants (of whom 1685 men) whose mean age was 43.6±11 years at baseline, and mean follow-up constituted 13.5±5.7 years (total 45.300 person-years). When 6.5% of participants with prevalent CHD were excluded, 3135 persons remained for analyses regarding incident CHD. Body height averaged 169.5±6.6 cm in men, 156.0±6.4 cm in women (median values were 170 and 156 cm, respectively).

Baseline characteristics of the total sample are shown in Table 1 stratified by sex and dichotomized body height. Short men and women were each significantly older ($p<0.05$) than tall individuals but no significant differences were observed among male groups with the exception of wider waist girths and higher family income in taller men. In contrast, except for serum HDL-cholesterol, apolipoprotein (apo) A-I and fasting glucose, all studied variables were significantly higher, while income and current smoking were lower in short compared with tall women.

Age-adjusted baseline characteristics are shown in Table 2 and Figure 1. Estimated marginal means for serum C3 were significantly higher and concentrations of triglycerides and CRP tended to be higher ($p=0.07$) in women (but not in men) with decreasing height tertiles. Men had higher waist circumference and triglycerides, and tended to had higher apo B and lower HDL-cholesterol with increasing height tertiles.

Prediction of outcome

Cox regression analyses for the prediction of overall mortality showing associations of body height are seen in Table 3 in three models each. In the age-adjusted model, overall mortality was significantly predicted by 1-SD increment (6.5 cm) in height in women alone (HR 0.83, [95% CI0.59; 0.98]). Non-linear relationship was detected in Model 2 using tertiles of height, adjusted for six further conventional risk factors (family income bracket, smoking status, alcohol usage, systolic blood pressure, serum HDL- and non HDL-cholesterol). Compared with tall women, females in lower two height tertiles had an over 2-fold risk of death. We tested whether this association was mediated by waist girth and CRP and reanalyzed by adding these to the previous model. Inclusion of CRP values (in part missing) limited the statistical power and thereby attenuated the significance of the association in women without altering the HRs. Male height exhibited a non-significant HR (of 1.05) for mortality in the two models and tended to be inversely associated in the model with added waist girth and CRP.

Regarding incident CHD (Table 4), height was not significantly associated in men in any of the three models, whereas height disclosed in women a modest insignificant inverse HR of 0.92 (95% CI 0.80; 1.05) in the age-adjusted model, failing to reach significance due to statistical power. The HR attenuated to 0.94 in the multiple-adjusted model and tended to strengthen when CRP was added to the regression model. The former model indicated a graded diminution of the HR with increasing height tertiles.

A search was made also with respect to incident stroke for which sex- and age-adjusted height displayed an HR of 1.08 (95% CI 0.82; 1.42) but this analysis with only 56 cases was underpowered (Table 5).

We excluded from the study sample all 322 deaths from causes other than cancer and analyzed sex-and age-adjusted mortality from cancer (86 cases). One-SD increment in height was associated with an HR 1.14 (95% CI 0.92; 1.44) in sexes combined. HR was positive in men 1.35 (95% CI 1.03; 1.77), non-significantly negative in women 0.82 (95% CI 0.55; 1.29). Adjustment

Table 1. Baseline characteristics of study sample by gender and dichotomized body height

Variables		Men (n=1685)				Women (n=1709)			
		Short ≤170 cm		Tall >170 cm		Short ≤156 cm		Tall >156 cm	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Height, cm	3394	165	3.9	174.4	4	151.7	3.7	161	3.9
Age, years	3394	**46.3[a]**	13.5	41	12.5	**46.5[a]**	13.7	40.7	12.4
Body mass index, kg/m^2	3394	25.7[c]	4	25.3	4	**28.7[a]**	6	26.6	5.2
Waist circumfer., cm	3362	93.2	10.7	**95.7[a]**	11.2	**91.8[a]**	12.8	89.8	12.7
Total cholesterol, mg/dL	3372	177.4	41	175	41	**188.8[a]**	41.7	179.3	41.6
F. triglycerides, mg/dL	2396	147.7	98	156.3	104	**136.7[a]**	93	116.2	70
HDL-cholesterol, mg/dL	3280	37.5	11.8	37.1	11.6	44.8	12.6	45	13
nonHDL-cholest., mg/dL	3351	140.4	41.4	138.2	42.4	**144[a]**	42.4	134.6	42.1
Fasting glucose, mg/dL	2905	93.6[c]	29.7	91	26.1	94.1	27.6	93.9	25.1
Apolipoprotein A-I, g/L	2098	1.26	.35	1.25	.29	**1.41**	.33	1.38	.33
Apolipoprotein B, g/L	2085	1.13	.34	1.16	.36	**1.16[b]**	.35	1.10	.37
C-reactive protein¶, mg/L	2686	2.04	3.2	1.93	3.1	**2.56[a]**	3.2	1.98	3.1
Fibrinogen, g/L	2221	2.98[c]	1.1	2.86	1.0	**3.24[b]**	1.1	3.09	1.0
Complement C3, g/L	1367	1.28	0.25	1.30	0.29	**1.36[b]**	0.29	1.32	0.27
Family income, I-V	3387	2.49	1.1	**3.01[a]**	1.16	2.41	1.19	**2.88[a]**	1.22
Current/form.smoker, n, %	3394	531/186	54/19	405/114	58/16	131/120	14/2%	163[a] /31	21/4%
Alcohol usage, y/n, %	3394	140	14.2%	140[b]	20.1%	3	0.3%	13[b]	1.6%

¶geometric mean values
Data are presented as mean and SD, proportion and percentage
*t-test for independent samples and Pearson's Chi-square test: p[a]<0.001, 0.01<[b]<0.05, 0.05<[c]<0.09
Circumfer. - circumference, chol. - cholesterol, F. - fasting, form. - former, HDL - high-density lipoprotein

Table 2. Certain age-adjusted baseline characteristics of study sample by gender and height tertiles

Variables		Men (n=1685)				Women (n=1709)			
	n	Short Mean	Medium Mean	Tall Mean	*p	Short Mean	Medium Mean	Tall Mean	*p
Height, cm	3394	162.6	169.9	176.7	<0.001	149.3	156.3	163.6	<0.001
nonHDL-C, mg/dL	3351	136.6	140.7	141.6	0.105	139.3	141.7	137.5	0.20
HDL-C, mg/dL	3280	38	36.5	37.5	0.10	44.3	45.6	44.7	0.19
Systolic BP, mmHg	3403	122	124	124	0.16	129	129	127	0.25
Complement C3, g/L	1367	1.27	1.30	1.30	0.50	1.37[c]	1.35	1.31	0.056
C3 adjusted for WC		1.29	1.30	1.28	0.83	1.37[a]	1.35	1.31	0.043
Apolipoprotein A-I, g/L	2098	1.26	1.25	1.27	0.68	1.42	1.37	1.40	0.14
Apolipoprotein B, g/L	2085	1.13	1.12	1.17	0.21	1.13	1.15	1.11	0.24

Data are presented as mean values
*ANOVA test with Tukey HSD tests; pairwise comparisons with Bonferroni adjustments: [a]p= 0.053, [b]=0.037 from that in tall women.
BP-blood pressure,C-cholesterol, HDL-high -density lipoprotein, WC-waist circumference

for multiple conventional risk factors including CRP attenuated the association to disappear in men (HR 1.04), and augmented in women the inverse association to 0.77 (95% CI 0.46; 1.29) suggesting that the height-related increased cancer death in men was largely mediated by CRP, but cancer mortality related to short stature in women might be independent of CRP.

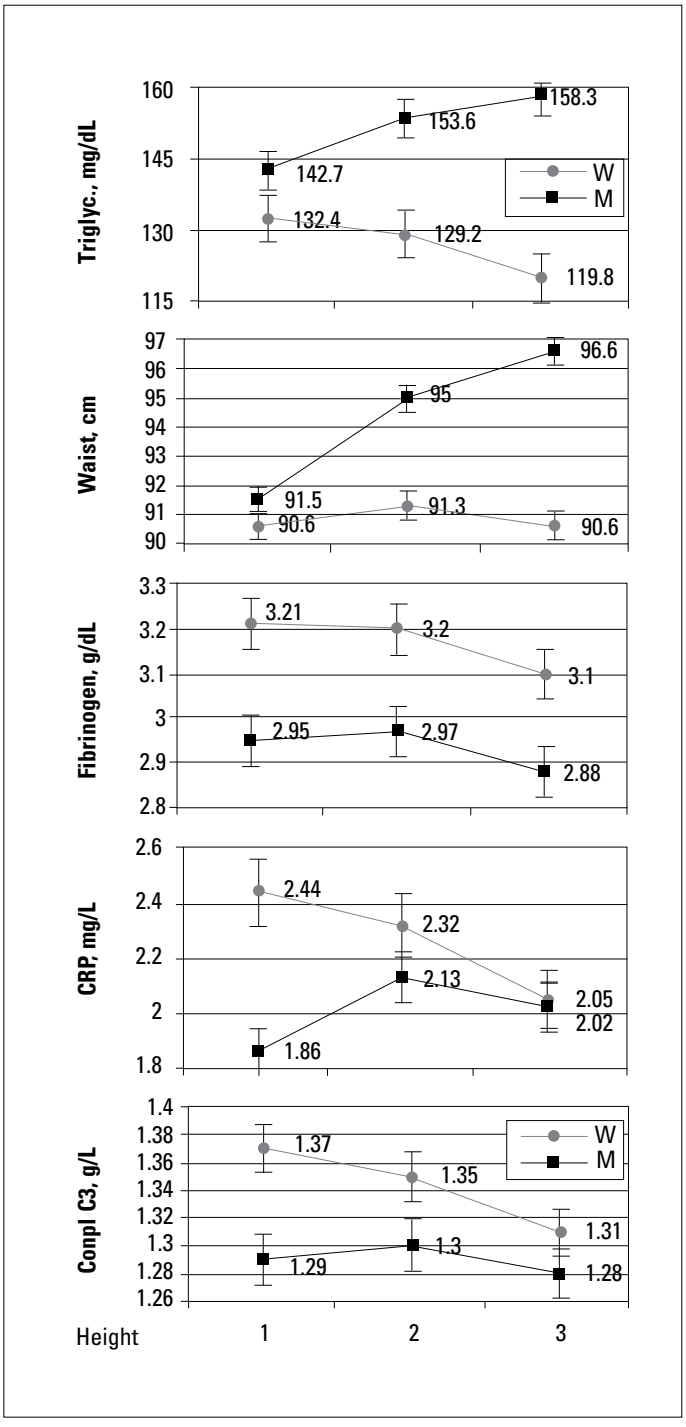

Figure 1. Association between mean height tertiles and certain risk factors adjusted to age 44 years in men and women. In men, waist circumference and triglycerides increase with rising height tertiles, whereas CRP, complement C3 (adjusted also for waist circumference) and fibrinogen do not vary appreciably with height. In women, diverging from men, though waist circumference and fibrinogen are similar at each height tertile, concentrations of complement C3 rise significantly and CRP and triglyceride increase (p=0.07 in each) with shorter height. CRP, complement C3 and triglycerides are exactly the three parameters which have been discerned in the TARF study as the clinical biomarkers of HDL dysfunction associated with enhanced low-grade inflammation

C3 - complement C3, CRP-C - reactive protein, HDL - high -density lipoprotein, Triglyc.- triglyceride

Discussion

In a prospective population-based study on a middle-aged adult sample having a high prevalence of MetS (44% at age 30 or over), we found a conspicuous gender difference in regard to both the covariates of body height and to the prediction of mortality and incident CHD. Estimated marginal means in women for serum triglycerides, CRP and C3 were higher with lower height tertiles, in contradistinction to men who had higher waist circumference and triglycerides, and tended to had higher apo B with increasing height tertiles. Likewise, height predicted all-cause death inversely in women and slightly tended weakly to do so for incident CHD. Male height, however, was not significantly associated with the studied outcomes. These findings suggested the interplay of a structural relationship insofar as mediators of inflammation (likely beyond CRP) were associated early in life with a short stature in women.

Associations of height with baseline variables

In men, waist circumference was significantly (by 5 cm) wider in the tall than the short group. This suggests that waist girth is related to body height, a fundamental relationship that has been noted in other ethnic populations though the slope of such a relationship is considerably diminished generally in women compared with men (The Emerging Risk Factors Collaboration. Adult stature and the risk of cause-specific death and vascular morbidity in 1 million people. 2011, as yet unpublished). Turkish women diverged from this and from Turkish men, inasmuch as they did not reveal narrower waists with shorter stature, implying the possibility of a structural relationship.

Age-adjusted analyses demonstrated that triglycerides, total cholesterol, diastolic BP and CRP tended to increase with rising height tertiles among men. These tendencies are likely secondary to a concomitantly rising waist circumference and might account for the marginally poorer outcome in males.

Age-adjusted analyses in women disclosed that triglycerides, C3 and CRP increased with shorter height, and fibrinogen tended to do so, suggesting that shorter women may have had early-life environments nurturing enhanced low-grade inflammation.

Gender difference

Essentially opposing trends emerged in the overall associations of the cardiovascular covariates of body height in the sexes as detailed above. These trends appeared translated into associations with outcomes of death and CHD, inasmuch as short stature was a significant risk factor for all-cause mortality (and tended to be so for incident CHD) in women, attenuating no more than marginally by adjustments for relevant factors.

In contrast, regarding male height that tended to be associated with slightly increased risk for both outcomes, adjustment of conventional risk factors fully attenuated the HR for CHD. This gender divergence might be related to the differing covariates of waist circumference in short stature.

Table 3. Cox regression analysis for prediction of all-cause death by body height and relevant covariates, in 3 models each

	Total		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI
Model 1		**408/3352†**		**245/1663†**		**163/1689†**
Gender, female	0.62	0.47; 0.83				
Height, 6.5 cm	0.97	0.88; 1.08	1.05	0.92; 1.20	0.83	0.59; 0.98
Age, 11 years	2.88	2.63; 3.18	2.63	2.33; 2.97	3.34	2.88; 3.91
Model 2		**364/3189†**		**217/1572†**		**147/1617†**
Gender, female	0.84	0.63; 1.11				
Height*, intermediate	1.27	0.91; 1.77	1.03	0.70; 1.53	2.13	1.10; 4.13
Height*, short	1.17	0.85; 1.61	0.92	0.62; 1.35	2.07	1.08; 3.97
Non-HDL-cholesterol, 35 mg/dL	1.07	1.00; 1.19	1.04	0.93; 1.19	1.15	1.00; 1.32
Systolic BP, 23 mmHg	1.38	1.26; 1.51	1.47	1.32; 1.69	1.26	1.02; 1.44
Current vs never smoking	1.54	1.16; 2.05	1.57	1.10; 2.22	1.48	0.87; 2.51
Alcohol intake, yes/no	1.39	0.98; 1.98	1.33	0.92; 1.92	0.00	too few deaths
Family income, I-V, per bracket	0.90	0.82; 0.99	0.91	0.80; 1.03	0.89	0.77; 1.02
Age, 11 years	2.36	2.13; 2.63	2.13	1.84; 2.43	2.77	2.36; 3.28
Model incl. CRP and waist		**235/2645†**		**145/1289†**		**90/1356†**
Height*, intermediate	1.02	0.65; 1.54	0.73	0.45; 1.20	2.13	0.93; 4.89
Height*, short	1.05	0.71; 1.55	0.76	0.47; 1.22	2.21	0.99; 4.98
CRP¶, mg/L	1.16	1.08; 1.25	1.17	1.07; 1.28	1.17	1.02; 1.33

¶Log-transformed values. Significant values are highlighted in bold. †-number of cases/number at risk
*Height referent ≥173 cm in men, ≥160 cm in women
Waist girth and HDL-cholesterol were not significant; former smoking was a significant predictor
(HR 2.54 [95% CI 1.03; 6.27]) of death in women
BP - blood pressure, CRP - C-reactive protein, HDL - high –density lipoprotein, HR- hazard ratio, expressed in terms of 1 SD for continuous variables

In a large study on Australasians, predominantly Asians, comprising nearly 4000 CHD and over 21.000 deaths (12), there was a 3% reduction in total mortality risk for each 1-SD increment in height in men, but not in women. With respect to CHD risk, as distinct from Australians, height was not related in female Asians and only borderline significantly associated in male Asians (HR 0.95 [95% CI 0.89; 1.01]). Stature was insignificantly associated positively with risk of CHD in over 15.000 Japanese middle-aged men and women (21) yet the study was underpowered for CHD events. Finally, regarding lower-extremity amputation among diabetic patients, body height remained a positive independent predictor (22).

Height in women inversely related to mortality

Association of height with overall mortality or CHD risk has not been consistent in women. Though the large Nurses' Health Study (1) found a HR of 0.73 (95% CI 0.65; 0.83) between the highest compared to the lowest group for CHD risk and the Renfrew/Paisley study (4) attained a similar HR for CHD mortality in women, other studies disclosed no significant independent relationship between height and all-cause mortality. Height was associated with mortality neither in men, nor in women in the NHANES I study (6). In the Eastern Finland survey, CHD mortality was inversely related with height in men but not women (9).

In the current study, the inverse age-adjusted association between height and all-cause death in women was no more than marginally attenuated by conventional socioeconomic, lifestyle, lipid and non-lipid risk factors suggesting that inflammatory mediators beyond CRP (perhaps complement activation, phospholipase A_2 enzyme, chemokines, adhesion molecules, etc. that affect macrophage recruitment into the arterial wall and possibly cancerogenesis) might be chiefly involved. It is further conjecturable that this process may be facilitated in women ethnically prone to short stature (such as Middle-Eastern women).

In contrast, and similar to the men of the British Regional Heart Study (3), the insignificantly elevated HR of height for CHD risk in men was fully attenuated by the above stated factors -consistent with the view that factors associated with a large waist girth concomitantly may mediate the CHD risk.

Table 4. Cox regression analysis for prediction of incident CHD by body height and relevant covariates, in 3 models each

	Total		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI
Model 1		**496/3135†**		**249/1541†**		**247/1594†**
Gender, female	0.94	0.79; 1.12				
Height*, intermediate	1.14	0.90; 1.45	1.22	0.88; 1.70	1.07	0.75; 1.52
Height*, short	1.02	0.80; 1.29	0.89	0.64; 1.24	1.17	0.83; 1.65
Age, 11 years	**1.94**	1.80; 2.08	**1.88**	1.67; 2.08	**1.80**	1.62; 2.00
Model 2		**479/2983†**		**242/1456†**		**237/1527†**
Gender, female	0.92	0.68; 1.24				
Height, 6.5 cm	0.96	0.87; 1.06	0.99	0.87; 1.14	0.94	0.81; 1.08
Systolic BP, 23 mmHg	**1.38**	1.26; 1.51	**1.54**	1.35; 1.73	**1.26**	1.12; 1.41
Non-HDL-cholesterol, 35 mg/dL	**1.32**	1.19; 1.42	**1.32**	1.19; 1.47	**1.32**	1.15; 1.47
HDL-cholesterol, 12 mg/dL	0.91	0.82; 1.00	**0.85**	0.74; 0.996	0.95	0.83; 1.09
Current vs never smoking	**1.29**	1.02; 1.65	**1.55**	1.12; 2.13	1.09	0.71; 1.67
Alcohol intake, yes/no	1.15	0.82; 1.60	1.11	0.79; 1.57	0.00	Few cases
Family income, I-V, per bracket	**0.91**	0.84; 0.99	0.94	0.84; 1.06	0.91	0.81; 1.01
Age, 11 years	**1.67**	1.52; 1.84	**1.61**	1.41; 1.82	**1.75**	1.54; 2.00
Model incl. CRP		**418/2504†**		**209/1216†**		**209/1288†**
Height, 6.5 cm	0.94	0.85; 1.05	0.98	0.85; 1.14	0.91	0.78; 1.06

Significant values are highlighted in bold. †-number of cases/number at risk
*Height referent ≥173 cm in men, ≥160 cm in women
BP - blood pressure, CHD - coronary heart disease, CRP - C-reactive protein, HDL - high -density lipoprotein, HR - hazard ratio, expressed in terms of 1 SD for continuous variables

Table 5. Logistic regression analysis for prediction of incident stroke by sex- and age-adjusted body height age-adjusted body height

	Total		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI
		56/3404†		**24/1682†**		**32/1722†**
Gender, female	0.64	0.29; 1.41				
Height, 6.5 cm	1.08	0.82; 1.42	1.12	0.74; 1.71	1.10	0.72: 1.51
Age, 11 years	**2.06**	1.61; 2.63	**2.63**	1.75; 3.99	**1.75**	1.27; 2.38

Significant values are highlighted in bold. †number of cases/number at risk
HR - hazard ratio, expressed in terms of 1 SD for continuous variables

Magnitude and shape of associations

All-cause mortality was increased with each decrement of 6.5 cm in height in women. This magnitude was stronger than the CHD risk association in the Nurses' Health Study (1) and considerably stronger than that in the Renfrew/Paisley study (4). It is remarkable that a threshold of 1.60 m existed also in the large Nurses' Health Study (1) which distinguished the two lowest of 5 categories of height. Similarly, a threshold (of 1.52 m) seems to be discernible in the study on over 340.000 South Korean women rather than a stated graded inverse association between height and total mortality (23) and in the comparatively small-sized study between short stature and cardiovascular disease (24). All-cause mortality expressed in terms of body height seems to be a composite of decreasing mortality of CHD and increasing one of cancer with increments of height (12, 25).

It is unclear why female height displayed a threshold below 1.60 m for overall mortality (or CHD risk). Acylation stimulating protein (ASP) is an adipose tissue-derived hormone that regulates triglyceride synthesis and glucose transport and is a precursor of complement C3. Correlations of ASP were opposite across genders with height, namely positive in Turkish men, inverse in women (26), suggesting that short women harbor higher amounts of ASP, paralleling the present finding of significantly higher age-adjusted C3 concentrations in shorter than

taller women. C3 activation leads to production of chemoattractants and C3 and its cleavage products link lipoprotein metabolism to immunity (27).

Genetic predisposition is a major determinant of height, yet rising stature across successive birth cohorts suggests that early life environment (in terms of nutrition, illness, socioeconomic status and psychosocial stress) also has an important impact (10). The inverse association between height and CHD death among monozygotic twin pairs discordant for such association suggested that direct environmental factors mediated this association (17). Protection was afforded by taller height in the Whitehall Study in participants with higher employment grades suggesting that childhood and adult social conditions may interact in their influence on coronary risk (5). In a sample including 865 nuclear families from the French Stanislas cohort, a familial clustering between height and cardiovascular risk factors were sought. No familial clustering between height and blood pressure was detected, but a cross-trait familial inverse correlation between height and LDL-cholesterol was consistent with a weak transmissible component of the relationship (16).

We have reported that Turkish women, far more than men, are inclined to have impaired function of HDL and its apolipoproteins as a major driver of risk of type-2 diabetes and CHD, which is attributable to enhanced low-grade systemic inflammation (28-30). The finding in the same female cohort that such factors are also likely linked to short stature associated with death in advanced adulthood suggests that a pronounced health problem of this adult population presumably has its roots in part in an adverse early childhood environment.

Study limitations

Certain limitations of the present study may be considered among which rank the relatively limited sample size and comparatively brief follow-up period, possibly valid especially for the fatal and nonfatal CHD risk which disclosed a lower hazard ratio rather than for total mortality that revealed a two-fold risk. The applicability of current major findings to different ethnicities may be limited in view of the high prevalence of the MetS and of HDL dysfunction, which constitute simultaneously the strengths of the study in terms of novel information. These include further the documentation of various covariates of height and the adjustments for a wide range of confounders in regression analyses of the associations with height, both of which revealed gender differences.

Conclusion

A gender difference clearly emerged in the association of body height with the prediction of mortality or incident CHD, which was not significant in men. In contrast, height marginally tended to predict incident CHD inversely in women and strongly predicted all-cause death, exhibiting a threshold. Both associations were not attenuated appreciably by adjustment of cardiovascular disease risk factors, the inflammation marker CRP and family income. Inflammatory mediators (beyond CRP) may be associated with a short stature gender-specifically early in life.

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