Height in relation to dementia death: individual participant meta-analysis of 18 UK prospective cohort studies

Tom C. Russ, Mika Kivimäki, John M. Starr, Emmanuel Stamatakis and G. David Batty

Background
That risk factors measured in middle age may not fully explain future dementia risk implicates exposures acting earlier in life. Height may capture early-life illness, adversity, nutrition and psychosocial stress.

Aims
To investigate the little-explored association between height and dementia death.

Method
Individual participant meta-analysis using 18 prospective general population cohort studies with identical methodologies (1994–2008; n = 181800).

Results
Mean follow-up of 9.8 years gave rise to 426 and 667 dementia deaths in men and women respectively. The mean heights were 174.4 cm (s.d. = 7.3) for men and 161.0 cm (s.d. = 6.8) for women. In analyses taking into account multiple covariates, increasing height was related to lower rates of death from dementia in a dose–response pattern (P<0.01 for trend). There was evidence of a differential effect by gender (P = 0.016 for interaction). Thus, the association observed in men (hazard ratio per s.d. decrease in height 1.24, 95% CI 1.11–1.39) was markedly stronger than that apparent in women (HR = 1.13, 95% CI 1.03–1.24).

Conclusions
Early-life circumstances, indexed by adult height, may influence later dementia risk.

Declaration of interest
None.

Method
Participants were taken from the Health Survey for England (HSE) for the years 1994–2008 and the Scottish Health Survey (SHS) for 1995, 1998 and 2003. Both surveys were representative, general population-based health examination studies sampling individuals living in households in the UK.13,14 From 1994 to 2008, 18 independent, cross-sectional studies with almost identical methodologies were conducted on either an annual (HSE) or an occasional (SHS) basis. The majority of study members (88%) consented to mortality surveillance by linkage to the UK National Health Service death register. The near-identical nature of these surveys, allied with this recent retrospective and prospective linkage of study members to mortality records, makes possible a unique individual participant meta-analysis. Study participants gave full informed consent, and ethical approval for data collection was granted by the London research ethics council or the local research ethics councils.

Participants were visited by a trained interviewer who measured height and weight, and subsequently by a nurse who collected biomedical data. The interviewer measured height once with shoes removed (to the nearest millimetre) with the informant stretching to maximum height. The head was positioned in the Frankfort plane and a portable stadiometer with a sliding plate, a base plate and three connecting rods marked with a metric measuring scale was used. Weight was measured using electronic digital scales and, with height, allowed computation of body mass index in kg/m². Information on occupational social class was
collected during the interview and coded according to the Registrar General’s classification (professional, intermediate, skilled non-manual, skilled manual, part skilled and unskilled), a standard approach in the UK.13 Age in years on leaving full-time education was recorded as <15, 15, 16, 17, 18, >18, ‘never went to school’ and ‘still in full-time education’. Ethnic group was based on self-report. Smoking status was classified as never a regular smoker, ex-smoker and smoker with daily consumption recorded.

During the interview participants were asked whether or not they suffered from a longstanding illness. At the nurse visit, systolic blood pressure was measured with the mean of the second and third readings used in the present analyses. Blood was drawn to measure serum cholesterol.

**Ascertainment of dementia**

Causes of death (up to ten) recorded on certificates were coded using the International Classification of Diseases (ICD-9 and ICD-10).16,17 Any mention of dementia death was identified using codes 290.0 to 290.4, 294.9, 331.0 to 331.2 and 331.9 for ICD-9 and codes F00, F01, F03, F09, G30 and G31 for ICD-10. In preliminary analyses we examined the impact of using broad definitions of dementia (any mention of dementia) or narrow definitions (where dementia was the underlying cause of death). Since results were essentially the same but the broader definition resulted in greater power (online Table DS1) we used ‘any mention’ of dementia in all survival analyses.

**Statistical analysis**

After ascertaining that the proportional hazards assumption had not been violated we used Cox proportional hazards models to compute study-specific hazard ratios with accompanying 95% confidence intervals for the association between height and dementia death.18 We report hazard ratios for height quartiles with the tallest group as the referent. With preliminary analyses revealing that the height–dementia association was linear, we also report hazard ratios per 1 standard deviation reduction in height (1 s.d. = 6.8 cm in women, 7.3 cm in men). Heterogeneity in the effect estimates between studies was examined using the $I^2$ statistic, which indicates the proportion of the total variation in the estimates that is due to between-studies variation. Preliminary analyses revealed that $I^2$ ranged between 0% and 58%, so we pooled the study-specific effect estimates and their standard errors in random effects meta-analyses, an approach we have taken in previous analyses.15,19,20 Calendar time (months) from survey date to record linkage were included in random effects meta-analyses, an approach we have taken in previous analyses.15,19,20 Calendar time (months) from survey date was the underlying time scale; for participants who did not die from dementia, data were censored at the end of March 2011.

Data for men and women were analysed separately. Models were initially adjusted for age and then additionally for a series of covariates comprising occupational social class, educational attainment, ethnic group, body mass index, smoking status and self-reported longstanding illness. We also controlled for birth year to allow for secular increases in height.21 Data for blood pressure and serum cholesterol were not collected in every survey (see online Table DS2) and were additionally missing for some participants during the survey years when data collection took place; these data therefore only feature in subgroup analyses. We compared the effects of controlling for different confounding and mediating variables on the magnitude of the association by examining the change in hazard ratio rather than a change in significance level.22 Individuals with data missing for one or more variables and those with no missing data were compared using Student’s $t$-test for continuous variables and $\chi^2$-tests for categorical variables. All analyses were conducted using R for Mac version 3.0.2. The reporting of our analyses conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.23

**Results**

Figure 1 shows the derivation of the analytical sample. Excluding 1840 individuals missing consent data and 1365 missing survival time reduced the sample size from 222,829 to 219,624. With other exclusions (survey participants who declined mortality follow-up or whose height was not measured) the final analytic sample was 181,800 (55% female). The mean age at baseline was 45.0 years (s.d. = 18.0); among those who died the mean age at death was 55.8 years (s.d. = 17.5). Further details of the individual cohort studies and individuals who did and did not consent to mortality follow-up are provided in online Tables DS2 and DS3 respectively.

Baseline characteristics of the sample categorised by height quartile are shown in Table 1. Increasing height was generally associated with a more favourable risk factor profile in both men and women: taller study members were younger, from higher socioeconomic backgrounds, had slightly lower body mass index, a lower prevalence of longstanding illness and lower levels of blood pressure and serum cholesterol. Taller men were also less likely to smoke, but the reverse was true of women. Of the 17,553 deaths recorded during a mean follow-up of 9.8 years (s.d. = 4.4), 1093 were dementia-related. Figure 2 shows the age-adjusted hazard ratios for the association between 1 s.d. decrease in height and dementia death in men and women for each cohort study. Overall, there was a 26% increased risk of dementia death per s.d. decrease in height in men (HR = 1.26, 95% CI 1.14–1.40; $P<0.001$ for trend) and 10% increased risk of dementia death in women (HR = 1.10, 95% CI 1.01–1.19; $P=0.031$ for trend). Table 2 shows the association between height quartile and dementia death after

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**Fig. 1 Flow chart of participants from initial pooled sample through to analytic sample showing subsequent mortality.**

<table>
<thead>
<tr>
<th>Original data-set</th>
<th>n = 222,829</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>n = 219,624</td>
</tr>
<tr>
<td>1840 missing consent data</td>
<td>1365 missing survival time</td>
</tr>
<tr>
<td>25,749 did not consent to record linkage</td>
<td></td>
</tr>
<tr>
<td>12,075 missing height data</td>
<td></td>
</tr>
<tr>
<td>Analytic sample</td>
<td>n = 181,800</td>
</tr>
<tr>
<td>Female participants</td>
<td>n = 99,467</td>
</tr>
<tr>
<td>Male participants</td>
<td>n = 82,333</td>
</tr>
<tr>
<td>8,556 deaths</td>
<td></td>
</tr>
<tr>
<td>8,997 deaths</td>
<td></td>
</tr>
<tr>
<td>667 dementia deaths</td>
<td></td>
</tr>
<tr>
<td>426 dementia deaths</td>
<td></td>
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</tbody>
</table>
We conducted a series of sensitivity and subgroup analyses to test the robustness of our results. Data were missing for one or more variables in 34,833 individuals (18%). Individuals with complete data for all variables are compared with those with any missing data in online Table D54. Although there were some differences in study characteristics, when we computed age-adjusted hazard ratios using a non-missing sample it replicated the main findings. Additionally, dropping deaths occurring in the first 5 years of follow-up to explore reverse causality did not alter our conclusions (Table 2).

### Sensitivity and subgroup analyses

We conducted a series of sensitivity and subgroup analyses to test the robustness of our results. Our main finding was a dose–response association between shorter height and risk of subsequent dementia death. There was some evidence of weaker associations in women than men: a formal test for effect modification was statistically significant at conventional levels (multivariable adjusted model $P = 0.016$ for interaction). Adjusting for measures of socioeconomic status had a modest attenuating effect on this association.

#### Discussion

Our main finding was a dose–response association between shorter height and risk of subsequent dementia death. There was some evidence of weaker associations in women than men: a formal test for effect modification was statistically significant at conventional levels (multivariable adjusted model $P = 0.016$ for interaction). Adjusting for measures of socioeconomic status had a modest attenuating effect on this association.

Fig. 2 Number of participants, total mortality and deaths from dementia categorised by year. Also shown are age- and gender-adjusted hazard ratios (HRs) of dementia death per standard deviation lower height according to survey year for (a) men and (b) women: individual participant meta-analysis of 18 cohort studies from the Health Survey for England (HSE) and the Scottish Health Survey (SHS).
suggestion that this relationship was stronger in men. It was robust to adjustment for a series of covariates including socio-economic status and extant illness. That we were also able to demonstrate known associations between shorter stature and an increased risk of cardiovascular disease (age- and gender-adjusted HR per s.d. decrease in height 1.11, 95% CI 1.07–1.16) but a decreased risk of cancer (HR=0.94, 95% CI 0.89–0.98) in this meta-analysis gives us confidence in the more novel height–dementia association.24–26

Mechanisms of effect

The fact that the observed association between height and dementia was apparently robust to the adjustment of a series of covariates leads to speculation regarding the mechanisms that might generate this relationship. Clearly height in itself is not a risk factor for dementia; rather, the exposures it captures may be key. In addition to genetic factors, a recent review of epidemiological studies highlighted various socio-environmental determinants of adult height, including early-life socioeconomic circumstances, childhood nutrition, chronic psychosocial stress and chronic illness.27 Insulin growth factor IGF-1 has been linked to cerebral amyloid deposition and, similarly, growth hormone levels, which are correlated with height and also linked to hippocampal function and cognition. Thus, IGF-1 might have a role in the association between height and dementia death.28 Furthermore, important exposures may also act in utero, but research linking birth characteristics to dementia is sparse. There is also the possibility that height might be a measure of cognitive and functional reserve,29 and a positive association has been demonstrated between height and intelligence,30 which is also related to dementia risk, particularly vascular dementia.31 A further possibility is a common genotype determining height and dementia risk. Average height in populations has generally increased in a secular fashion over the past century, with a marked increase in the first quarter of the 20th century (Fig. 3). The fact that there has been a general improvement in early-life circumstances over the same period supports the hypothesis that height captures something of early-life experience relevant to later dementia risk, particularly in the light of recent studies suggesting that the prevalence of dementia might have decreased in recent years.32

Comparison with other literature

The published research on the association between stature and dementia risk is detailed in online Table DS5. Our study is the first to examine the association between stature and dementia mortality. However, for comparison, research reporting on the association with clinical dementia is discussed here. In a Medicare study of the association between knee height and arm span and...
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dementia in four areas of the USA, 480 participants developed dementia over a mean 5.4 year follow-up.12 Both measures of shorter stature were associated with a higher risk of dementia in women, but only arm span was associated with dementia risk in men. A study in Israel only of men demonstrated an odds ratio of dementia (309 cases) comparing the tallest and shortest height quartiles of 0.51 (95% CI 0.35–0.74) after adjusting for age, socioeconomic status and region of birth. A study of Japanese Americans in Washington, USA, as part of the Ni-Hon-Sea Project – mainly focusing on head circumference – similarly commented that individuals developing dementia (59 incident cases) were shorter than those who did not go on to develop the condition. However, this was not examined in detail.32

Cross-sectional studies also add to the evidence for a link between height and dementia. A study of an older Korean population (n = 746, 110 dementia cases) found an association between shorter leg length and demispan and dementia after adjusting for age and education.33 When men and women were considered separately results were statistically significant only in women, but since only 41% of the sample were men this might have been a result of reduced power. Another Korean study (n = 235, with 46 dementia cases) found an association between decreased height and increased dementia risk (age- and gender-adjusted HR per cm decrease 1.09, 95% CI 1.05–1.14), which was attenuated with further adjustment for education, smoking, alcohol, pulse pressure, hypertension and type 2 diabetes mellitus (HR = 1.03, 95% CI 0.97–1.11).28 The HARMONY study of Swedish twins conducted a case–control analysis of 310 people with dementia and 3063 controls.34 They found that being more than 1 s.d. below the gender-specific mean in height was associated with an odds ratio of dementia of 1.57 (95% CI 1.11–2.22). A case–control study from the USA found a lower risk of Alzheimer’s disease in women, adjusted for age and education, but not men.35 However, when they stratified by APOE e4 status they found this association only in women without that allele (OR = 0.88, 95% CI 0.80–0.97). A further Korean study found an association, only in women, between leg length and Alzheimer’s disease, after adjustment for age, rural residence in childhood and education.36

There is growing evidence – from studies of variable quality and statistical power – that shorter body stature, measured in a variety of ways, is associated with an increased risk of cognitive decline and dementia in men and women. A number of studies have reported a dose–response association,11,12,35,37 but the majority have treated height as a continuous measure without demonstrating a linear relationship.28,32,33,36,38,39 We were able to demonstrate a statistically significant, dose–response association between decreasing height and dementia death. One prospective study and two cross-sectional studies showed a stronger association between height and dementia in women than in men.12,33,36 We found the converse. It is possible that this disagreement relates to power or to the different outcomes: the studies referred to above used a clinical diagnosis of dementia as their outcome, as opposed to dementia-related death used in our study. Details of dementia incidence were not available for our included cohort studies. We are not aware of any studies directly comparing risk factors for dementia incidence and dementia-related mortality.

Limitations
Our large sample was representative of the general population in the UK and was well characterised in terms of baseline

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**Fig. 3** Secular trend (with 95% confidence interval) in height according to birth year: 18 cohort studies from the Health Survey for England and Scottish Health Survey.
and the Department of Epidemiology and Public Health at University College London. Currently employed by the University of Edinburgh and the UK NHS, T.C.R. was supported by Alzheimer Scotland during the preparation of this manuscript. T.C.R., J.M.S. and G.D.B. are members of both the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland and the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (G0700704/48849). Funding from the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, the Economic and Social Research Council (ESRC) and the UK Medical Research Council (MRC) is gratefully acknowledged. E.S. is funded by a National Institute for Health Research Career development fellowship and M.K. is supported by the MRC (K070351), the US National Institutes of Health (R01HL036310, R01AG034545) and a professional fellowship from the ESRC.

Implications of the study

We have demonstrated a dose-response association between height and later dementia risk which was robust to adjustment for a series of covariates. We propose the hypothesis that the mechanism driving this association may be early-life circumstances and thus add to the growing evidence of the role of pre-adult factors in later dementia risk. Furthermore, public health policies need to take this association into account. In the absence of such a study, a more detailed investigation of just what it is that height is capturing that is associated with later dementia risk would allow more accurate forecasts of dementia incidence to be calculated.

Future research directions

Ideally, a long-term longitudinal study with adult height and relevant covariates measured in early life could be analysed over decades of follow-up to investigate this association in more detail, including information on parental height in order to take genetic determinants of height into account. In the absence of such a study, a more detailed investigation of just what it is that height is capturing that is associated with later dementia risk would allow more accurate forecasts of dementia incidence to be calculated.

References

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