ORIGINAL ARTICLE

Midlife blood pressure predicts future diastolic dysfunction independently of blood pressure

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on behalf of the MRC NSHD Scientific and Data Collection Team

ABSTRACT

Objectives High blood pressure (BP) is associated with diastolic dysfunction, but the consequence of elevated BP over the adult life course on diastolic function is unknown. We hypothesised that high BP in earlier adulthood would be associated with impaired diastolic function independent of current BP.

Methods Participants in the Medical Research Council National Survey of Health and Development birth cohort (n=1653) underwent investigations including echocardiography at age 60–64 years. The relationships between adult BP, antihypertensive treatment (HTT) and echocardiographic measures of diastolic function were assessed using adjusted regression models.

Results Increased systolic BP (SBP) at ages 36, 43 and 53 years was predictive of increased E/e’ and increased left atrial volume. These effects were only partially explained by SBP at 60–64 years and increased left ventricular mass. HTT was also associated with poorer diastolic function after adjustment for SBP at 60–64 years. Faster rates of increase in SBP in midlife were also associated with increased poorer diastolic function.

Conclusions High SBP in midlife is associated with poorer diastolic function at age 60–64 years. Early identification of individuals with high BP or rapid rises in BP may be important for prevention of impaired cardiac function in later life.

INTRODUCTION

With an ageing population, and better postmyocardial infarction survival, the burden of congestive heart failure is increasing and represents a major public health challenge.1 Diastolic dysfunction is common in people over 45 years with a prevalence of 28% in a large community study,2 and is a precursor of heart failure with preserved ejection fraction (HFPEF).2 Echocardiographic measures of diastolic dysfunction and elevated left ventricular (LV) filling pressure also predict a threefold increased cardiac mortality and a twofold increased all-cause mortality in those with normal ejection fractions.2 3 High systolic blood pressure (SBP) is an important cause of diastolic dysfunction, and there is evidence that raised antecedent SBP in early and midadulthood is associated with increased risk of heart failure,4 and elevated risk of cardiovascular mortality independent of current blood pressure (BP).4 However, there has been limited work investigating the effects of longitudinal changes in BP over adulthood on diastolic function.6 We have previously shown that increased SBP in adult midlife is associated with increased LV mass in later life independent of later SBP and that rapid rises in midlife SBP might play a key role.7 We hypothesised that a similar relationships may exist between SBP and diastolic function and also aimed to determine the extent to which this might be due to increased LV mass. In addition, we examined the association between antihypertensive treatment (HTT) and subsequent diastolic function.

METHODS

Study patients

The UK Medical Research Council National Survey of Health and Development (MRC NSHD) is a prospective birth cohort study of singleton births that occurred in 1 week of March 1946 in England, Scotland and Wales (5362 births; 2547 women, 2815 men). Follow-up has included over 20 contacts with the whole cohort between birth and the most recent data collection when the participants were between 60 and 64 years of age.7

Study members still alive and with a known current address in England, Scotland or Wales were invited for an assessment at one of six clinical research facilities (CRFs) or to be visited by a research nurse at home. Invitations were not sent to those who had died (N=778), who were living abroad (N=570), had previously withdrawn from the study (N=594) or had been lost to follow-up (N=564). Of the 2856 invited participants, 2229 (78%) were assessed: 1690 (59%) attended a CRF and the remaining 539 were visited at home. Echocardiography was only carried out at the CRF (N=1653). The participating sample remains broadly representative of native born British men and women of the same age.8

Ethical approval was obtained from the Central Manchester Research Ethics Committee (07/H1008/168) and the Scotland A Research Ethics Committee. Written informed consent was obtained from each study member at each stage of data collection.

Anthropometry and BP measurement

Height and weight were measured at the clinic visit and body mass index (BMI) calculated. Sitting brachial BP was measured in the upper right arm with an appropriately sized cuff after 5 min of rest at 53 years and 60–64 years with the second
measurement used in analyses, or the first measure where the
second was missing. A Hawksley random zero sphygmomanom-
eter (Hawksley & Sons, Lincin, UK; a state of the art machine
at the time) was used at 36 and 43 years.5 6 A validated oscillo-
metric device (Omron HEM-705) was used in later in home
visits. To enable comparison of BP measured by the different
machines, the measurements from the random zero sphygmo-
manometer were adjusted using published conversion
equations.10

Antihypertensive treatment and diabetes status
Prior to clinic attendance, study members completed a postal
questionnaire that included details of current medication.
Antihypertensive medications for the last two rounds were clas-
sified according to International Classification of Diseases and
related Health Problems classification.21 Self-reported and
doctor diagnosed type 2 diabetes mellitus (T2DM) was obtained
from the postal questionnaires and reports at earlier follow-ups.

Echocardiography
Of the 1690 participants who attended a clinic, 1653 (798 men
and 855 women, mean age 63.3±1.1 years (ISD)) underwent
echocardiography using GE Vivid I machines (GE, Connecticut,
USA) and 1576 had at least one analysable image (95%).
Echocardiographic images were obtained from parasternal long
axis and short axis, apical five-chamber, four-chamber, three-
chamber, two-chamber and aortic views along with conventional
tissue Doppler and Doppler in the four-chamber view. Image analysis
was carried out by three experienced British Society of
Echocardiography-accredited readers including the author
(AGK) masked to patient identity using GE EchoPac software.
The following markers of diastolic function were measured in
accordance with American Society of Echocardiography/
European Association of Echocardiography recommendations—
ratio of early (E) to late (A) transmitral Doppler flow (E/A),
early (e') myocardial velocity at the mitral valve annulus
(average of septal and lateral wall measures) e', E/e' and ratio of
early and late (a') myocardial velocities at the mitral valve
annulus (average of septal and lateral wall measures) e'/a'.12 E/e'
was calculated as an estimate of LV filling pressure.12 Left atrial
volume indexed to body surface area (LAVI) was also examined as
a marker of chronically elevated LV filling pressures.13

Quality control measures included standardised training
for senior, experienced echocardiographers and readers, echocardi-
ographer observation by trained echocardiographers, periodic
reader and echocardiographer review and refresher sessions,
phantom studies on ultrasound machines and continuous quality
control audit throughout the period of data collection. Blind
duplicate reading reproducibility studies (n=70 on two occasions)
were carried out to establish inter-reader and intrareader variabil-
ity. These showed excellent reproducibility (intraclass correlation
coefficients were >0.90 for most measurements).

Statistical analysis
Statistical analysis was performed using Stata V14.1 (StataCorp
LP, USA). Initially, separate regression models investigated the
association between SBP at each of the 4 ages at which it was
measured and measures of diastolic function at 60–64 years,
with adjustment for sex, age at clinic visit and clinic attended.
We examined whether associations were linear by inspection of
residuals. Given evidence that cardiac function may differ by
sex,7 we also investigated whether associations with SBP were
subject to effect modification by sex through inclusion of a
sex×SBP term in models, but this was not statistically significant
in any model. Consequently, we show data from models includ-
ing both sexes that were adjusted for sex. HTT at the same age
as BP measurement was then added to the models. Additional
models assessed whether earlier SBP remained predictive once
current SBP was also included, that is, to what extent antecedent
SBP was independent of current SBP. This is an important con-
sideration given the anticipated correlations between SBP at dif-
ferent times within an individual (tracking). Further statistical
models were constructed by including potential confounders
BMI, T2DM, smoking and physical activity status at age 60–64
years. In a further model left ventricular mass indexed to body
surface area (LVMI) was included with possible confounders to
exploit the extent to which LVMI might mediate the associa-
tions observed.

In order to maintain the sample size and minimise bias intro-
duced by missing data in fully adjusted analyses, we employed a
multiple imputation procedure to impute missing covariates. For
each outcome, a total of 20 imputed datasets were obtained
using chained equations implemented using imputation by
chained equations in Stata. For the imputation models we
included all variables in the final adjusted analytic model, each
model, as well as the outcome and additional variables that
helped predict the missing covariates. The regression coefficients
and standard errors were calculated for each imputed dataset,
and then combined using Rubin’s rule.

To investigate whether rate of change in SBP at a particular
period of midlife was more strongly associated with diastolic
function, we calculated the change in SBP for the periods 36–43
years, 43–53 years and 53–60/64 years conditional on earlier
SBP by modelling each SBP measure (from age 43 years on
the earlier measure(s) for each sex and saving the residuals. These
residuals reflect SBP velocity and can be interpreted as the
change in SBP in an individual above or below that expected on
average in the sample given their earlier SBP.14 The residuals
were standardised (mean=0 and SD=1) to allow a comparison
of the relative strength of associations between periods. We sub-
sequently fitted regression models including all these standard-
dised changes with each of the measures of diastolic function as
the outcome. This analysis was performed only for individuals
who had all variables observed (complete case analysis). Two
models were constructed: model 1—adjusted for age, sex and
CRF attended; model 2—model 1+T2DM+BMI+smoking
status+physical activity status+current HTT. p Values were cal-
culated using Wald tests. Similar analyses were repeated for dia-
stolic BP (DBP), pulse pressure (PP) and mean arterial pressure
(MAP).

Sensitivity analyses were carried out to assess whether the
associations with SBP remained unchanged if those who were
hypertensive (SBP≥140 mm Hg or DBP≥90 mm Hg) were
excluded.

RESULTS
Characteristics of participants with any echocardiography data
at age 60–64 years are shown in table 1. Those with unanalys-
able echocardiograms had higher BMIs and heart rates, but BP
did not differ.7 Additional participant characteristics are pre-
semed in online supplementary table S1.

SBP from age 53 years was negatively associated with e'
(table 2). This relationship weakened with progressive risk
factor adjustment. HTT was negatively associated with e' in the
minimally adjusted model from age 53 years.

Broadly similar findings were observed when the associations
between current and antecedent SBP and E/A were examined,
although relationships tended to be weaker. SBP at 53 and

60–64 years was predictive of E/A and HTT at any age was unrelated to E/A (table 3). Data relating SBP measured at various ages to e′/a′ were consistent with observations for e′ and E/A (data not shown).

SBP from 36 years onwards was positively associated with increased E/e′ (table 4). The relationship persisted after adjustment for age, sex, clinic attended, current HTT/SBP/BMI/T2DM/smoking/physical activity. SBP at age 53 years and HTT at age 53 years were also positively associated with LAVI (table 5). Analyses were repeated replacing SBP with DBP, PP or MAP should similar associations (data not shown).

From 43 years onwards, those on HTT had increased E/e′; this was not affected substantively by adjustment for current SBP; regression coefficients were slightly attenuated by adjustment for BMI/T2DM/smoking/physical activity although relationships remained statistically significant (table 4). We also investigated whether the effect of earlier SBP was mediated via LV hypertrophy by inclusion of LVMI into regression models. This was not the case.

We investigated whether relationships between elevated BP in earlier life and e′ and E/e′ might be driven by inclusion of people who went on to develop hypertension. However, when those who were hypertensive at 60–64 years (SBP ≥140 mm Hg or DBP ≥90 mm Hg) were excluded from the analysis, the associations remained very similar (data not shown).

We looked to see whether there was a sensitive period when rate of change in SBP had most influence on diastolic function and filling pressure. Increased rates of rise in SBP over the age periods 43–53 and 53–60/64 years were also significantly associated with worse e′ (figure 1A) and E/A (figure 1B). Increased rate of rise in SBP at all age periods (36–43 years, 43–53 years and 53–60/64 years) was associated with increased E/e′ (figure 1C), although the relationship was strongest over the period 43–53 years in the minimally adjusted model. The rate of rise in the 43–53 years period was also associated with increased LAVI (figure 1D).

DISCUSSION
BP from early midlife predicted worse diastolic function and evidence of elevated filling pressure at age 60–64 years. This effect was independent of current BP extended across the whole range of BP, and was not limited to people with hypertension or those who went on to develop hypertension at the time when diastolic function was assessed. We observed that those on HTT from early midlife had poorer diastolic function than those not on HTT even after current BP was accounted for. Further, we found that individuals showing comparatively rapid rises in SBP between 43–53 years and 53–60/64 years had worse subsequent diastolic function irrespective of their absolute level of SBP. Since the rise in BP in the UK population typically begins to accelerate around the fourth decade of life until it slows again in later life,15 we suggest that the period 40–60 years may represent a sensitive period when an accelerated rise in BP adversely influences future development of diastolic dysfunction.

There has been limited work in the past on relating antecedent BP with future diastolic function. Arnlov et al reported that higher SBP and DBP at the age of 50 years were associated

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**Table 1** Echocardiographic and cardiac risk factor characteristics of study participants

<table>
<thead>
<tr>
<th>Variable (at age 60–64 years unless stated otherwise)</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Result</td>
<td>n</td>
<td>Result</td>
</tr>
<tr>
<td>Age, years</td>
<td>1626</td>
<td>63.2 (1.1)</td>
<td>786</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1633</td>
<td>27.7 (4.6)</td>
<td>791</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>1633</td>
<td>135.7 (18.0)</td>
<td>791</td>
</tr>
<tr>
<td>SBP in those on HTT, mm Hg</td>
<td>347</td>
<td>137.4 (17.4)</td>
<td>179</td>
</tr>
<tr>
<td>SBP in those not on HTT, mm Hg</td>
<td>1120</td>
<td>134.9 (18.0)</td>
<td>518</td>
</tr>
<tr>
<td>SBP in those with unknown HTT status, mm Hg</td>
<td>166</td>
<td>137.4 (18.6)</td>
<td>92</td>
</tr>
<tr>
<td>SBP at age 53 years, mm Hg</td>
<td>1537</td>
<td>134.3 (19.1)</td>
<td>738</td>
</tr>
<tr>
<td>SBP at age 43 years, mm Hg</td>
<td>1522</td>
<td>123.7 (14.1)</td>
<td>735</td>
</tr>
<tr>
<td>SBP at age 36 years, mm Hg</td>
<td>1479</td>
<td>120.0 (13.7)</td>
<td>714</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>1633</td>
<td>77.3 (9.7)</td>
<td>791</td>
</tr>
<tr>
<td>DBP at age 53 years, mm Hg</td>
<td>1537</td>
<td>83.5 (11.9)</td>
<td>738</td>
</tr>
<tr>
<td>DBP at age 43 years, mm Hg</td>
<td>1522</td>
<td>80.5 (9.5)</td>
<td>735</td>
</tr>
<tr>
<td>DBP at age 36 years, mm Hg</td>
<td>1477</td>
<td>78.3 (9.6)</td>
<td>713</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>1630</td>
<td>68.9 (11.2)</td>
<td>789</td>
</tr>
<tr>
<td>IVSD, cm</td>
<td>1473</td>
<td>1.1 (0.2)</td>
<td>701</td>
</tr>
<tr>
<td>PWT, cm</td>
<td>1471</td>
<td>1.0 (0.2)</td>
<td>699</td>
</tr>
<tr>
<td>RWT</td>
<td>1469</td>
<td>0.4 (0.1)</td>
<td>699</td>
</tr>
<tr>
<td>LVMI, g</td>
<td>1471</td>
<td>181.3 (59.3)</td>
<td>699</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>1471</td>
<td>95.7 (26.6)</td>
<td>699</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>1459</td>
<td>68.7 (9.7)</td>
<td>692</td>
</tr>
<tr>
<td>E/A</td>
<td>1576</td>
<td>1.0 (0.3)</td>
<td>755</td>
</tr>
<tr>
<td>e′, cm/s</td>
<td>1533</td>
<td>8.8 (1.9)</td>
<td>727</td>
</tr>
<tr>
<td>E/e′</td>
<td>1490</td>
<td>7.9 (2.1)</td>
<td>701</td>
</tr>
<tr>
<td>e′/a′</td>
<td>1507</td>
<td>0.8 (0.2)</td>
<td>709</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>1417</td>
<td>21.1 (7.2)</td>
<td>701</td>
</tr>
</tbody>
</table>

Data are mean (SD), median (interquartile range) or n (%) as appropriate.

BMI, body mass index; DBP, diastolic blood pressure; IVSD, interventricular septal thickness in diastole; LAVI, left atrial volume indexed to body surface area; LVMI, left ventricular mass; LVM, left ventricular mass indexed to body surface area; PWT, left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; SBP, systolic blood pressure.

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Table 2  Regression between e′ at 60–64 years and SBP and antihypertensive treatment at four time points with further adjustment for covariates

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)×10^-3 p Value</td>
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<td>β (95% CI)×10^-3 p Value</td>
<td>β (95% CI)×10^-3 p Value</td>
</tr>
<tr>
<td>Age 36 (n=1533) SBP</td>
<td>−0.006 (−0.014 to 0.002) 0.125</td>
<td>−0.006 (−0.014 to 0.002) 0.122</td>
<td>−0.001 (−0.009 to 0.007) 0.855</td>
<td>−0.002 (−0.010 to 0.006) 0.619</td>
<td>0.000 (−0.008 to 0.008) 0.931</td>
</tr>
<tr>
<td>Age 43 (n=1533) SBP</td>
<td>−0.006 (−0.013 to 0.002) 0.128</td>
<td>−0.005 (−0.012 to 0.002) 0.171</td>
<td>0.002 (−0.007 to 0.010) 0.598</td>
<td>0.001 (−0.007 to 0.008) 0.816</td>
<td>0.000 (−0.009 to 0.008) 0.959</td>
</tr>
<tr>
<td>Age 53 (n=1533) SBP</td>
<td>−0.011 (−0.017 to −0.006) &lt;0.001</td>
<td>−0.010 (−0.016 to −0.005) &lt;0.001</td>
<td>−0.005 (−0.011 to 0.001) 0.084</td>
<td>−0.004 (−0.010 to 0.002) 0.157</td>
<td>−0.002 (−0.006 to 0.009) 0.694</td>
</tr>
<tr>
<td>Age 60–64 (n=1533) SBP</td>
<td>−0.017 (−0.022 to −0.012) &lt;0.001</td>
<td>−0.017 (−0.022 to −0.011) &lt;0.001</td>
<td>NR</td>
<td>NR</td>
<td>−0.015 (−0.020 to −0.009) &lt;0.001</td>
</tr>
<tr>
<td>Age 60–64 HTT NR</td>
<td>0.112 (−0.846 to 1.070) 0.819</td>
<td>0.018 (−0.937 to 0.973) 0.971</td>
<td>0.039 (−0.910 to 0.989) 0.935</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Age 60–64 HTT NR</td>
<td>−0.619 (−1.296 to 0.058) 0.073</td>
<td>−0.598 (−1.271 to 0.075) 0.081</td>
<td>−0.495 (−1.163 to 0.173) 0.146</td>
<td>−0.403 (−1.064 to 0.257) 0.231</td>
<td>−0.094 (−0.340 to 0.152) 0.453</td>
</tr>
</tbody>
</table>

Imputed (n=1533 for all models—with valid outcome and SBP at age 60–64 years). The variable β is regression coefficient for e′ versus SBP (mm Hg) or antihypertensive treatment (HTT). Model 1: adjusted for age sex and CRF attended. Model 2: model 1 + antihypertensive treatment (HTT) at given age (for SBP) or model 1+SBP at given age (for HTT). Model 3: model 2+SBP at 60–64 years. Model 4: model 3+T2DM+BMI+smoking status—physical activity status. Model 5: model 4+left ventricular mass indexed to body surface area. Numbers of individuals receiving HTT were 51 (2%), 107 (3%), 438 (15%) and 640 (27%) at age 36, 43, 53 and 60–64 years, respectively.

BMI, body mass index; CRF, clinical research facility; NR, not relevant; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Table 3  Regression between E/A at 60–64 years and SBP and antihypertensive treatment at four time points with further adjustment for covariates

<table>
<thead>
<tr>
<th>Independent variable</th>
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<th>Model 3</th>
<th>Model 4</th>
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<tr>
<td></td>
<td>β (95% CI)×10^-3 p Value</td>
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<td>β (95% CI)×10^-3 p Value</td>
<td>β (95% CI)×10^-3 p Value</td>
</tr>
<tr>
<td>Age 36 (n=1576) SBP</td>
<td>0.3 (−0.8 to 1.5) 0.564</td>
<td>0.3 (−0.8 to 1.4) 0.598</td>
<td>0.9 (−0.2 to 2.1) 0.116</td>
<td>0.8 (−0.4 to 1.9) 0.190</td>
<td>0.8 (−0.3 to 2.0) 0.170</td>
</tr>
<tr>
<td>Age 43 (n=1576) SBP</td>
<td>0.4 (−0.7 to 1.4) 0.481</td>
<td>0.4 (−0.6 to 1.5) 0.443</td>
<td>1.3 (0.2 to 2.3) 0.024</td>
<td>1.1 (0.06 to 2.2) 0.039</td>
<td>1.2 (0.1 to 2.2) 0.036</td>
</tr>
<tr>
<td>Age 53 (n=1576) SBP</td>
<td>−1.4 (−2.2 to −0.7) &lt;0.001</td>
<td>−1.5 (−2.3 to −0.7) &lt;0.001</td>
<td>−1.0 (−1.8 to −0.1) 0.025</td>
<td>−0.7 (−1.5 to 0.1) 0.099</td>
<td>−0.7 (−1.5 to 0.2) 0.118</td>
</tr>
<tr>
<td>Age 60–64 (n=1576) SBP</td>
<td>−1.8 (−2.6 to −1.1) &lt;0.001</td>
<td>−1.8 (−2.6 to −1.0) &lt;0.001</td>
<td>NR</td>
<td>NR</td>
<td>−1.5 (−2.2 to −0.7) &lt;0.001</td>
</tr>
<tr>
<td>Age 36 HTT NR</td>
<td>0.7 (−0.8 to 2.2) 0.356</td>
<td>0.39 (−0.89 to 0.207) 0.430</td>
<td>59 (−89 to 207) 0.338</td>
<td>70 (−73 to 214) 0.338</td>
<td>70 (−74 to 241) 0.339</td>
</tr>
<tr>
<td>Age 43 HTT NR</td>
<td>−35 (−137 to 62) 0.443</td>
<td>−36 (−133 to 61) 0.464</td>
<td>−27 (−131 to 77) 0.613</td>
<td>−17 (−127 to 93) 0.761</td>
<td>−6 (−82 to 85) 0.059</td>
</tr>
<tr>
<td>Age 53 HTT NR</td>
<td>−27 (−16 to 70) 0.221</td>
<td>25 (−18 to 69) 0.248</td>
<td>40 (−3 to 83) 0.067</td>
<td>42 (−2 to 85) 0.059</td>
<td>42 (−2 to 85) 0.059</td>
</tr>
<tr>
<td>Age 60–64 HTT NR</td>
<td>−25 (−58 to 9) 0.149</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.4 (−33 to 35) 0.936</td>
</tr>
</tbody>
</table>

Imputed (n=1576 for all models—with valid outcome and SBP at age 60–64 years). The variable β is regression coefficient for E/A versus SBP (mm Hg) or antihypertensive treatment (HTT). Model 1: adjusted for age sex and CRF attended. Model 2: model 1+HTT at given age (for SBP) or model 1+SBP at given age (for HTT). Model 3: model 2+SBP at 60–64 years. Model 4: model 3+T2DM+BMI+smoking status—physical activity status. Model 5: model 4+left ventricular mass indexed to body surface area. Numbers of individuals receiving HTT were 51 (2%), 107 (3%), 438 (15%) and 640 (27%) at age 36, 43, 53 and 60–64 years, respectively.

BMI, body mass index; CRF, clinical research facility; NR, not relevant; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
Table 4  Regression between E/e' at 60–64 years and SBP and antihypertensive treatment at four time points with further adjustment for covariables (n=1490 for all models—with valid outcome and SBP at age 60–64 years)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>p Value</td>
<td>β (95% CI)</td>
<td>p Value</td>
<td>β (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Age 36 (n=1490) SBP</td>
<td>0.015 (0.006 to 0.024)</td>
<td>0.001</td>
<td>0.015 (0.006 to 0.024)</td>
<td>0.001</td>
<td>0.007 (−0.002 to 0.016)</td>
<td>0.118</td>
</tr>
<tr>
<td>Age 36 (n=1490) SBP</td>
<td>0.019 (0.011 to 0.027)</td>
<td>&lt;0.001</td>
<td>0.017 (0.009 to 0.025)</td>
<td>&lt;0.001</td>
<td>0.008 (0.000 to 0.017)</td>
<td>0.052</td>
</tr>
<tr>
<td>Age 36 (n=1490) SBP</td>
<td>0.022 (0.017 to 0.028)</td>
<td>&lt;0.001</td>
<td>0.020 (0.014 to 0.026)</td>
<td>&lt;0.001</td>
<td>0.013 (0.007 to 0.019)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 60–64 (n=1490) SBP</td>
<td>0.024 (0.019 to 0.030)</td>
<td>&lt;0.001</td>
<td>0.023 (0.018 to 0.029)</td>
<td>&lt;0.001</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Age 36 HTT NR</td>
<td>−0.06 (−1.18 to 1.06)</td>
<td>0.917</td>
<td>0.06 (−1.05 to 1.18)</td>
<td>0.909</td>
<td>0.004 (−1.08 to 1.09)</td>
<td>0.994</td>
</tr>
<tr>
<td>Age 43 HTT NR</td>
<td>1.38 (0.62 to 2.13)</td>
<td>&lt;0.001</td>
<td>1.34 (0.59 to 2.08)</td>
<td>&lt;0.001</td>
<td>1.13 (0.39 to 1.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age 53 HTT NR</td>
<td>0.72 (0.39 to 1.05)</td>
<td>&lt;0.001</td>
<td>0.72 (0.39 to 1.04)</td>
<td>&lt;0.001</td>
<td>0.62 (0.30 to 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 60–64 HTT NR</td>
<td>0.69 (0.44 to 0.95)</td>
<td>&lt;0.001</td>
<td>NR</td>
<td>NR</td>
<td>0.55 (0.29 to 0.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The variable β is regression coefficient for E/e' versus SBP (mm Hg) or antihypertensive treatment (HTT). Model 1: adjusted for age sex and CRF attended. Model 2: model 1+HTT at given age (for SBP) or model 1+SBP at given age (for HTT). Model 3: model 2+SBP at 60–64 years. Model 4: model 3+T2DM+BMI+smoking status+physical activity status. Model 5: model 4+left ventricular mass indexed to body surface area. Numbers of individuals receiving HTT were 51 (2%), 107 (3%), 438 (15%) and 640 (27%) at age 36, 43, 53 and 60–64 years, respectively.

CRF, clinical research facility; E/e', estimated e' (m/s); HTT, antihypertensive treatment; NR, not relevant; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Table 5  Regression between LAVI at 60–64 years and SBP and antihypertensive treatment at four time points with further adjustment for covariables (n=1417 for all models—with valid outcome and SBP at age 60–64 years)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>p Value</td>
<td>β (95% CI)</td>
<td>p Value</td>
<td>β (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Age 36 (n=1417) SBP</td>
<td>0.042 (0.013 to 0.072)</td>
<td>0.005</td>
<td>0.041 (0.012 to 0.071)</td>
<td>0.006</td>
<td>0.035 (0.004 to 0.065)</td>
<td>0.025</td>
</tr>
<tr>
<td>Age 43 (n=1417) SBP</td>
<td>0.042 (0.013 to 0.070)</td>
<td>0.004</td>
<td>0.040 (0.011 to 0.069)</td>
<td>0.006</td>
<td>0.021 (0.001 to 0.061)</td>
<td>0.042</td>
</tr>
<tr>
<td>Age 53 (n=1417) SBP</td>
<td>0.056 (0.036 to 0.075)</td>
<td>&lt;0.001</td>
<td>0.047 (0.027 to 0.068)</td>
<td>&lt;0.001</td>
<td>0.043 (0.021 to 0.065)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 60–64 (n=1417) SBP</td>
<td>0.030 (0.009 to 0.051)</td>
<td>0.004</td>
<td>0.028 (0.008 to 0.050)</td>
<td>0.007</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Age 36 HTT NR</td>
<td>2.560 (−1.650 to 6.771)</td>
<td>0.232</td>
<td>2.769 (−1.433 to 6.971)</td>
<td>0.195</td>
<td>1.931 (−2.262 to 6.124)</td>
<td>0.365</td>
</tr>
<tr>
<td>Age 43 HTT NR</td>
<td>2.179 (−0.393 to 4.751)</td>
<td>0.097</td>
<td>2.205 (−0.352 to 4.762)</td>
<td>0.091</td>
<td>1.388 (−1.204 to 3.981)</td>
<td>0.293</td>
</tr>
<tr>
<td>Age 53 HTT NR</td>
<td>2.304 (1.139 to 3.469)</td>
<td>&lt;0.001</td>
<td>2.326 (1.161 to 3.491)</td>
<td>&lt;0.001</td>
<td>1.979 (0.799 to 3.159)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age 60–64 HTT NR</td>
<td>1.290 (0.667 to 2.512)</td>
<td>0.001</td>
<td>NR</td>
<td>1.084 (0.134 to 2.033)</td>
<td>0.025</td>
<td>0.645 (−0.466 to 1.371)</td>
</tr>
</tbody>
</table>

The variable β is regression coefficient for LAVI versus SBP (mm Hg) or antihypertensive treatment (HTT). Model 1: adjusted for age sex and CRF attended. Model 2: model 1+HTT at given age (for SBP) or model 1+SBP at given age (for HTT). Model 3: model 2+SBP at 60–64 years. Model 4: model 3+diabetes mellitus+body mass index+smoking status+physical activity status. Model 5: model 4+left ventricular mass indexed to body surface area. Numbers of individuals receiving HTT were 51 (2%), 107 (3%), 438 (15%) and 640 (27%) at age 36, 43, 53 and 60–64 years, respectively.

CRF, clinical research facility; LAVI, left atrial volume indexed to body surface area; NR, not relevant; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
with decreased E/A measured 20 years later in the Swedish Uppsala cohort. Hypertension is thought to cause diastolic dysfunction via impaired LV relaxation and reduced LV compliance. Ultimately, the elevated filling pressures associated with severe diastolic dysfunction can lead to HFPEF or pulmonary oedema. Interestingly, Lee et al reported that higher BP and BMI in midlife were predictive of incident heart failure in later life in the Framingham study. Our data suggest that this relationship may be mediated at least in part via diastolic dysfunction.

Randomised clinical trials such as Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Hypertension in the Very Elderly Trial (HYVET) have demonstrated the benefits of treating hypertension in terms of decreased incidence of new heart failure and heart failure admissions. However, optimal management of diastolic dysfunction remains unclear: trials in HFPEF have demonstrated little or no benefit with conventional heart failure medication. There is evidence for improvement in diastolic function with short-term HTT, but longer-term HTT was not associated with improvement of diastolic function despite regression of LV mass in a substudy of the Anglo Scandinavian Cardiac Outcomes trial. Nevertheless, BP control is considered a cornerstone of management of these patients. In our cohort we found that from 43 years onwards, for any given level of BP (including for BP in the normal range, those on HTT had worse diastolic function at 60–64 years). The residuals can be interpreted as the standardised rate of change in SBP in an individual above or below that expected on average in the sample given their earlier SBP. (A) e′ at age 60–64 years (n=1172). (B) E/A at age 60–64 years (n=1190). (C) E/e′ at age 60–64 years (n=1120). (D) Left atrial volume indexed to body surface area at age 60–64 years (n=1054). Data points are β coefficients and the bars represent 95% CIs. Model 1 (●): adjusted for age, sex and clinical research facility attended. Model 2 (○): model 1+diabetes mellitus+body mass index+smoking status+physical activity status+current antihypertensive treatment. p Values were calculated using Wald tests and p<0.05 indicates a significant association between the rate of change in SBP in the specified period and the measure of diastolic function.

Figure 1 Association between standardised residuals of change in systolic blood pressure (SBP) over three time periods (36–43 years), (43–53 years) and (53–60 to 64 years) conditional on the earlier measure(s) markers of diastolic function at age 60–64 years. The residuals can be interpreted as the standardised rate of change in SBP in an individual above or below that expected on average in the sample given their earlier SBP. (A) e′ at age 60–64 years (n=1172). (B) E/A at age 60–64 years (n=1190). (C) E/e′ at age 60–64 years (n=1120). (D) Left atrial volume indexed to body surface area at age 60–64 years (n=1054). Data points are β coefficients and the bars represent 95% CIs. Model 1 (●): adjusted for age, sex and clinical research facility attended. Model 2 (○): model 1+diabetes mellitus+body mass index+smoking status+physical activity status+current antihypertensive treatment. p Values were calculated using Wald tests and p<0.05 indicates a significant association between the rate of change in SBP in the specified period and the measure of diastolic function.
Strengths and limitations
Our findings are derived from a nationally representative sample of native-born British people born in 1946.8 Using the life course approach in relating BP at different ages and change in BP over time to future diastolic function is unique and is a major strength of our study. This was only possible due to detailed repeated measurements of risk factors and recording of HTT in our study, which is the longest running birth cohort in the UK. Studies of birth cohorts have a number of advantages, notably that accounting for the effect of age is much less problematic. We used tissue Doppler as our primary measure of diastolic function, this has the advantage that it can distinguish normal diastolic function from pseudonormalisation.30 Pseudonormalisation will tend to attenuate relationships between antecedent BP and diastolic function assessed by E/A, and probably accounts for the generally weaker relationships seen using this measure of diastolic function. Missing data are inevitable in studies as long-running as the MRC NSHD (>60 years), although participant retention was good in comparison with other cohorts.11 Compared with those study members who attended clinic for clinical examination and echocardiography, those who only had clinical examinations at home visits had higher BMI and heart rates. However, participation of relatively more healthy individuals in the echocardiography study is, if anything, likely to have weakened relationships between BP and diastolic function. There were no measurements of BP prior to 36 years, and hence we cannot comment on the importance of BP in earlier life periods. We are limited to identifying a sensitive period from three intervals as the study has only four measures of BP. This lack of BP measurements in limits our ability to determine whether BP control was optimal between measurements. Echocardiography was only carried out in the last round of data collection; hence the possibility of diastolic dysfunction preceding the rise in BP cannot be excluded, although such a relationship seems unlikely.

CONCLUSIONS
BP from the age of 36 years predicts diastolic dysfunction in people aged 60–64 years independently of current BP (for E/e’ and LAVI); faster increases in BP in midlife are particularly detrimental. People on HTT have more adverse diastolic function even when current BP is taken into account suggesting that early risk factor modification may be important to prevent the adverse effects of BP on diastolic function.

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Contributors AKG, RH and ADH conceived and designed the research and carried out the statistical analyses. DK secured funding for the study. All authors critically reviewed the manuscript. AKG, ADH and RH are responsible as guarantors for the overall content.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

Key messages
What is already known on this subject?
► High blood pressure (BP) is associated with diastolic dysfunction in cross-sectional studies.
► Very little is known about the longitudinal effects of high BP and changes in BP over adult life on future diastolic function.

What might this study add?
► High blood pressure (BP) levels, and rises in BP in midadulthood adversely affect diastolic function up to 28 years later.
► Hypertensive individuals have worse diastolic function even when current BP was taken into account.

How might this impact on clinical practice?
► Early identification of those with fast rising blood pressure (BP) (even in the ‘normal’ BP range) may be important to prevent diastolic dysfunction in later life.

Cardiac risk factors and prevention


Midlife blood pressure predicts future diastolic dysfunction independently of blood pressure

Arjun Kumar Ghosh, Alun David Hughes, Darrel Francis, Nishi Chaturvedi, Denis Pellerin, John Deanfield, Diana Kuh, Jamil Mayet and Rebecca Hardy

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