Cross-sectional association of blood pressure variability and night-time dipping with cardiac structure in adolescents

Goudswaard, BP variability and dipping in adolescents

LJ Goudswaard (BSc)1,2,3*, S Harrison (PhD)2,3, D Van De Klee (MBChB MRCGP)4, N Chaturvedi5 (MBBS MRCP MFPHM MSc MD), DA Lawlor (MSc MBChB PhD MPH MRCGP MFPHM)2,3, G Davey Smith (MA MD BChir MSc)2,3, AD Hughes (BSc MBBS PhD)5, LD Howe (BSc MSc PhD)2,3

1 – School of Physiology, Pharmacology and Neuroscience at the University of Bristol
2 – MRC Integrative Epidemiology Unit at the University of Bristol
3 – Population Health Sciences, Bristol Medical School, University of Bristol
4 – Acute GP Team, BrisDoc Healthcare Services
5 - Institute of Cardiovascular Science, University College London

* Corresponding author, and requests for reprints: Lucy Goudswaard, Population Health Sciences, Oakfield House, Oakfield Grove, Bristol BS8 2BN. Email: lg14289@bristol.ac.uk, telephone: +44 (0)117 3311448

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Greater blood pressure variability (BP) and reduced night-time BP dipping are associated with cardiovascular disease independently of mean BP in adults. This study examines whether these associations are apparent in adolescents. A cross-sectional analysis was undertaken in 587 UK adolescents. We examined associations between measures of blood pressure dipping and variability (including standard deviation weighted for day/night (SDdn), average real variability (ARV) and variability independent of the mean (VIM)) with cardiac structure measures assessed by echocardiography: (1) left ventricular mass indexed to height$^{2.7}$ (LVMi$^{2.7}$), (2) relative wall thickness (RWT), (3) left atrial diameter indexed to height (LADi), and (4) left ventricular internal diameter in diastole (LVIDD). Greater BP variability was associated with cardiac structures including higher RWT, which persisted after adjustment for mean BP. There was no evidence for an association between night-time dipping and cardiac structures. Measurement of BP variability might benefit cardiovascular risk assessment in adolescents.

Introduction

Higher blood pressure (BP) is associated with an increased risk of cardiovascular disease (CVD) $^1$. However, BP is inherently variable, and under a typical circadian rhythm night-time BP is lower than daytime $^2$. Loss of this nocturnal dipping pattern in the adult general population of adults has been shown to be associated with cardiovascular events and all-cause mortality, independent of 24-hour BP $^2, 3$. In
addition, there is also evidence that non-circadian variability in BP may be associated with cardiovascular disease ², ⁴, ⁵.

Cardiovascular pathology starts in early life: childhood BP levels are known to track across life ⁶ and early adulthood BP associates with CVD mortality ⁷. In adults, higher left ventricular (LV) mass and left atrial enlargement are both associated with higher risk of CVD ⁸, ⁹ and are considered evidence of target organ damage ¹⁰. Another measure of left heart function, relative wall thickness (RWT, a measure of remodelling¹¹), has been suggested to be predictive of stroke among adult populations¹², ¹³. We previously demonstrated that in 17 year-olds that higher body mass index (BMI) is causally related to higher LV mass indexed to height², ⁷ (LVMi², ⁷)¹⁴, suggesting that there is meaningful variation in cardiac structure measures in early adulthood. A study in adults from the general population indicated a positive association between BP variability and LVMi ¹⁵. However, it is not known whether 24-hour BP variability and night-time dipping in adolescents are related to cardiac structure.

In this study, we used data from a prospective cohort study of 587 UK adolescents to assess the cross-sectional associations of mean BP (from clinic measurements and ambulatory monitoring), BP variability, and night-time dipping, with measures of cardiac structure at age 17, determined by echocardiography. The measures of cardiac structure we consider are 1) LV mass (LVM), 2) RWT ¹¹, 3) left atrial diameter (LAD), and 4) left ventricular internal diameter during diastole (LVIDD, a measure of the initial stretching of cardiomyocytes before contraction (preload)) ¹⁶. Together these
represent a comprehensive assessment of left heart structure, with functional significance\textsuperscript{17}.

**Results**

*Participant characteristics*

A total of 587 participants were included in our analysis. Figure 1 shows how this cohort size was reached from the participants enrolled in ALSPAC at baseline. Compared with the full ALSPAC cohort, the participants included in our analysis tended to have mothers who were more educated and older when the participant was born and be from a family with a higher head of household occupational social class; females were also more likely to be included. Clinic blood pressure, minutes of moderate to vigorous physical activity at age 15 and DXA-determined fat mass were similar compared with the full ALSPAC cohort (Supplementary Table 1).

Of the included participants, 43.1\% were male, mean age was 17.7 (SD 0.3) years, 2.1\% reported smoking 1 or more cigarettes a week. Mean clinic systolic and diastolic blood pressure were 114.4 mmHg (SD 9.7 mmHg) and 64.5 mmHg (SD 5.8 mmHg), respectively (table 1). 22.3\% of participants were categorised as non-dippers for systolic BP, and 6.3\% for diastolic BP. Mean LVM\textsuperscript{2.7} was 27.7 g/m\textsuperscript{2.7} (SD 5.9 g/m\textsuperscript{2.7}), LADi was 1.88 cm/m (SD 0.22 cm/m), LVIDD was 4.52 cm (SD 0.44 cm) and RWT was 0.37 (SD 0.06).

Males tended to have higher systolic blood pressure, pulse pressure and mean arterial pressure, while females had higher diastolic blood pressure. Night-time dipping was similar between sexes. Males tended to have higher systolic and diastolic BP
variability than females. Ventricular measures were higher in males, while atrial index and wall thickness were similar between sexes (Table 1).

1) Associations between clinic BP measurements and cardiac structures

Clinic SBP was associated with higher LVMi2.7 (β = 0.23 SDs per SD increase in SBP, 95% CI 0.15 to 0.32, P=1.6x10^-7) and higher RWT (β = 0.29 SDs per SD increase in SBP, 95% CI 0.19 to 0.39, P=1.2x10^-8) after adjustment for confounders (Table 2).

There was no evidence of associations with LADi or LVIDD.

Clinic DBP was associated with higher RWT (β = 0.24, 95% CI 0.15 to 0.33, P=1.4x10^-7) and lower LADi and LVIDD. There was no evidence of an association between clinic DBP and LVMi2.7.

Results were broadly similar in the age and sex only adjusted models (Supplementary Table 2).

Associations between ambulatory averages of BP and cardiac structures

There was evidence of a positive association between 24-hour mean SBP and LVMi2.7 (β = 0.17 SDs per SD higher 24-hour SBP, 95% CI 0.093 to 0.25, P=1.8x10^-5), which was slightly smaller in magnitude than the association for clinic SBP (Figure 2).

Daytime and night-time means for SBP also showed positive associations with LVMi2.7, with similar magnitudes to 24-hour mean SBP. The 24-hour mean SBP also showed a positive association with RWT (β = 0.18, 95% CI 0.089 to 0.26, P=8.1x10^-5), with similar magnitudes of association seen for daytime and night-time mean SBP. There was no evidence of associations between 24-hour, day-time or night-time mean SBP and LADi or LVIDD.
There was evidence for associations between all 24-hour DBP measures (mean, day and night) and RWT, with similar magnitudes of associations between the three exposures, but no evidence of associations for the other measures of cardiac structure.

2) Associations between 24-hour blood pressure variability and cardiac structures

ARV of SBP was associated with LVMi\(^2.7\) after adjustment for confounders (Table 2). All three measures of SBP variability (SDdn, ARV, VIM) were positively associated with RWT (SBP SDdn and RWT: \(\beta = 0.15\), 95% CI 0.061 to 0.23, \(P=7.9 \times 10^{-4}\)). There was no consistent evidence of associations between SBP variability and LADi or LVIDD. DBP variability measures were positively associated with RWT, although evidence of association was weaker for VIM than for SDdn and ARV. ARV and VIM of DBP were also positively associated with LVMi\(^2.7\) and LADi.

After further adjustment for 24-hour BP (Table 3), associations of SBP and DBP variability with LVMi\(^2.7\) and RWT attenuated towards the null. Some associations with RWT remained: before adjustment for mean DBP the standardised association between ARV of DBP and RWT was 0.13 (95% CI 0.045 to 0.21, \(P=2.7 \times 10^{-3}\)). After adjustment for mean DBP it was 0.11 (95% CI 0.022 to 0.19, \(P=0.014\)).

3) Associations between night-time BP dipping and cardiac structures

The results provided no evidence for associations between either of the dipping variables (percentage difference and categorical) and cardiac structures (Supplementary Table 2, Table 2, Table 3). This was true for both SBP and DBP.
Complete case analysis

For all analyses, there were similar magnitudes of estimates between the complete cases and imputed analyses (Supplementary Table 3 and Table 3). However, as there was less power in the complete case analysis, confidence intervals were wider.

Discussion

In this cross-sectional study of a general population of adolescents, we have shown that average 24-hour and clinic SBP are generally positively associated with echocardiographic measures of cardiac structure such as LVMi2.7 and RWT in adolescents after adjustment for confounders. Average 24-hour and clinic DBP generally showed positive associations with RWT, but not with other cardiac structure measures. Clinic BP and average 24-hour measures from ABPM showed similar associations with all cardiac outcome measures. Measures of 24-hour variability (SDdn and ARV) were positively associated with RWT for both SBP and DBP. ARV of both SBP and DBP were also positively associated with LVMi2.7. Some of these associations persisted after adjustment for 24-hour mean BP, including the associations of ARV of DBP with RWT. No associations were found between night-time dipping and cardiac structure.

Variability in BP over 24 hours in this sample of adolescents was similar in magnitude to that reported in studies of adults38,39. In contrast, the percentage of normal dipping was higher than in adult studies26. In adults, greater variability in BP and non-dipping...
are associated with cardiovascular risk, independently of average BP \(^2, 26, 40, 41\). Higher visit-to-visit BP variability in children has been shown to be associated with adult hypertension in the Bogalusa Heart Study \(^42\). Two previous studies, restricted to hypertensive children, did not find an association between 24-hour BP variability and LVM\(^2, 7\) \(^43, 44\). Similarly, several studies have found little association between night-time dipping and LVMi in hypertensive children \(^25, 45, 46\). To our knowledge, this is the first study to explore these associations in a general population cohort of adolescents.

Higher mean SBP is associated with higher LVMi\(^2, 7\) and RWT in our study. This finding, together with our previous finding that higher BMI is causally related to higher LV mass \(^14\), suggests that higher values of LVMi\(^2, 7\) and RWT are, on average, related to adverse cardiovascular health even in this young population, rather than due to high levels of fitness. This implies that the cardiac structures are meaningful markers of cardiac health in this young population. Both DBP and SBP were associated with RWT to a similar extent. However, unlike SBP, DBP did not show associations with LVMi\(^2, 7\). This could reflect a greater importance of systolic pressure (and by implication pulse pressure on LV mass) or it may be at least partially driven by regression dilution bias because of the greater levels measurement error for DBP compared with SBP \(^47\).

Our results indicate that some associations between greater BP variability and cardiac structure remained once average BP was accounted for, such as diastolic measure of ARV with RWT. These findings support the notion that the influence of BP variability on cardiac structure may begin early in life\(^42\). We found no convincing evidence of an association between non-dipping and cardiac structure in young people. Findings in older adults are inconsistent \(^48\) and most studies finding a positive association between
non-dipping and LV mass have been conducted in hypertensive individuals. The majority of the participants in our sample had blood pressures in the normal range; other studies which included such participants have also not found evidence of an association.

Previous research used smaller participant numbers than the current study and tended to focus on hypertensive children. It is possible that our study may have lacked statistical power to detect some associations between BP variability and dipping and cardiac structure independently of mean BP. However, this is the only available dataset with a highly detailed range of clinic and ABPM measurements for each participant in this age group. One of the strengths of our analysis is the inclusion of adolescents from the general population which provides a more representative sample of UK adolescents. A possible limitation, however, is that the cohort are of European descent and in a localised area of the UK, which may limit its external validity.

Our study uses cross-sectional data from a birth cohort study. This limits our ability to determine the true direction of the association between blood pressure and cardiac structures, and whether this relationship may be causal. The participants included in our analysis are more affluent than the full ALSPAC cohort. However, whilst this does affect the generalizability of the study, it does not necessarily lead to bias in the estimates of associations. There is some evidence that lack of generalisability on cohort studies does not bias exposure-outcome associations.

Another possible limitation of this study is that ABPMs affect sleep quality due to the cuff inflating throughout the night, which may affect night-time dipping levels. A
previous study found that those with lower quality of sleep had higher nocturnal BP levels and a smaller BP dip; this could weaken associations. Despite this limitation, a recent large cohort study has confirmed that 24-hour ambulatory blood pressure monitoring is a stronger predictor of cardiovascular and all-cause mortality than clinic measurements, confirming the validity of its use.

Our results show that, in adolescents, higher clinic and 24-hour SBP and DBP, as well as an increase in blood pressure variability, are associated with more adverse cardiac structure. Non-dipping was not found to be associated with cardiac structure. Our study implies that measurement of BP variability, but not night-time dipping, might add to the assessment of cardiovascular risk in adolescents. However, this finding would benefit from replication in larger studies. It would be valuable to explore whether BP variability and dipping in adolescents track across the life course, and whether these BP measurements in adolescents are predictive of longer-term cardiovascular outcomes.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be submitted via the Avon Longitudinal Study of Parents and Children (ALSPAC) website http://www.bristol.ac.uk/alspac/researchers/access/.

Participants

ALSPAC is a population-based birth cohort. The study recruited pregnant women from the Avon area (Bristol) in the South West of England, with an expected delivery date
between 1\textsuperscript{st} April 1991 and 31\textsuperscript{st} December 1992 \textsuperscript{18}. From the 15,643 pregnant women enrolled, 14,889 children were born and alive at one year \textsuperscript{18,19} (Figure 1). Since birth, participants have been followed up, using questionnaires, links to routine data, and research clinics. The study website provides further details of the cohort and a data dictionary \url{http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/}.

Approval was obtained from the local ethics committee and the ALSPAC Law and Ethics committee.

\textit{Inclusion/Exclusion Criteria}

This was a cross-sectional study conducted in participants who attended the 17-year follow-up clinic of ALSPAC. Participants were eligible if they attended both the echocardiography and the 24-hour blood pressure sub-studies at the 17-year clinic visit (N=587). They were excluded if they were pregnant or reported having a congenital cardiac anomaly.

\textit{Exposures}

1) \textit{Clinic and 24-hour ambulatory blood pressure measurements}

Clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an OMRON 705 IT with the participant sitting and at rest with their arm supported. We used the average of the final two measures from the right arm in our analyses.

Participants were fitted with a 24-hour ambulatory blood pressure monitor (ABPM) (Spacelabs 90217, Washington, U.S.) according to the manufacturer’s instructions. This measured their brachial BP, with readings taken every 30 minutes during the day
and hourly at night. Participants were permitted to perform usual physical activities, although a diary of activities was recorded. Daytime and night-time were defined by the participant. The expected maximum number of total readings per participant therefore varied depending on the duration of the night-time period. For this study, we included participants with at least 14 readings during the self-defined daytime and at least 5 readings during the self-defined night-time \(^{20, 21}\).

We estimated the mean 24-hour SBP and DBP using the ABPM data, and also estimated the daytime and night-time means for SBP and DBP.

2) **Measures of blood pressure variability**

Since there is disagreement in the literature about the most appropriate measures of BP variability, and since the importance of different variability measures in the adolescent population is not known, we estimate variability in the 24-hour systolic and diastolic measures in three different ways. 1) Standard deviation weighted for daytime and night-time (SDdn)\(^{22}\), calculated as: 
\[
\frac{(day \ SD \times \ day \ hours) + (night \ SD \times \ night \ hours)}{day \ hours + night \ hours}.
\]

2) Average real variability (ARV), derived as the average of the differences between consecutive BP measurements\(^{23}\), using the formula: 
\[
\frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|,
\]

where \(N\) is the number of valid blood pressure (BP) readings. 3) Variability independent of the mean (VIM)\(^{24}\), derived using the formula: 
\[
\frac{SD_{dn}}{\text{mean}^{x}} \times \text{population mean}^{x},
\]

where \(x\) is derived from the regression coefficient \(\beta\) from the equation: 
\[
\ln(SD) = \alpha + \beta \ln(\text{mean}).
\]

3) **Dipping variables**
We estimated night-time dipping as a percentage difference between daytime and night-time means \((\frac{24\text{hr daytime BP} - 24\text{hr nighttime BP}}{24\text{hr daytime BP}} \times 100)\). We considered participants with \(\geq 10\%\) reduction in night-time BP compared to daytime BP as ‘normal dippers’, and those with \(<10\%\) reduction or an increase as ‘non-dippers’ in a binary dipping variable\(^3\)\(^{,25}\). We also grouped participants into four dipping groups of 1) Normal dippers (>10%, \(\leq 20\%\)), 2) Non-dippers (>0%, \(\leq 10\%\)), 3) Extreme dippers (>20%) and 4) Risers (<0%) to allow comparison of dipping distribution with previous studies\(^{26}\), however only the simpler continuous and dichotomised variables are included as an exposure in our analyses because of the relatively small sample size.

**Outcomes: Echocardiography Measurements**

Echocardiography was performed on a quasi-random subsample (based on date of research clinic attendance) using an HDI 5000 ultrasound machine (Philips, Massachusetts, U.S.) equipped with a P4-2 Phased Array ultrasound transducer. One of two echocardiographers examined participants using a standard examination protocol, in accordance with the American Society of Echocardiography (ASE) guidelines. All measures were made in end diastole and were calculated as the mean of three measurements. LV mass was calculated from end-diastolic ventricular septal wall thickness (SWTd), left ventricular dimension (LVIDd), and left ventricular posterior wall thickness (PWT) according to the ASE formula: \(0.8 \times (1.04 \times [(\text{SWT} + \text{LVIDD} + \text{PWT})^3 - (\text{LVIDD})^3]) + 0.6\). LV mass was then indexed to height\(^2\)\(^,7\) (LVMi\(^2\)\(^,7\)) using the Troy formula in order to account for differences in body sizes \(^{27}\). Left atrial diameter was indexed to height \(^9\) (LADi). Relative wall thickness (RWT) was calculated using the formula: \(\frac{\text{PWT} + \text{SWT}}{\text{LVIDD}}\).
Confounders:

We considered variables as confounders if they had plausible relations with BP and cardiovascular risk\textsuperscript{28}. Maternal confounders were self-reported in questionnaires completed during pregnancy: educational attainment (categorised as university degree or higher, Advanced-levels (exams usually taken around 18 years and necessary for university entry), Ordinary-levels (exams usually taken around 16 years, which was the minimum UK school leaving age at the time these participants were this age), or lower than Ordinary-levels, including vocational education); pre-pregnancy body mass index (BMI; in kg/m\textsuperscript{2}); age at delivery (categorised as <25 years, 25-35 years, and >35 years); parity, and highest head of household occupational social class. We selected these maternal variables as the mother’s socioeconomic position (SEP) represents the participant’s family SEP. SEP has been shown to influence BMI (a key determinant of both BP and LVM\textsuperscript{14}), blood pressure\textsuperscript{29}, and left ventricular structure\textsuperscript{30}. Maternal pre-pregnancy BMI has also been shown to affect offspring BP and cardiovascular outcomes\textsuperscript{31}.

Child-based confounders were from a combination of self-reported questionnaire and clinic-based data: age (in months) at year 17 clinic visit; smoking at age 17 (<1 or ≥1 cigarette per week from self-report); minutes of moderate to vigorous physical activity at age 15 assessed by uniaxial ActiGraph accelerometer (Florida, U.S.) and used as quintiles in the analysis; percentage fat mass (assessed by dual energy-X-ray absorptiometry (DXA) at the 17-year clinic using a Lunar prodigy narrow fan beam densitometer); and height measured at the 17-year clinic using a Harpenden stadiometer (Holtain Ltd, Crymych, UK).
Statistical analysis:

All analyses were performed using Stata version 15.1 (StataCorp, TX). We used multivariable linear regression to estimate the associations between all blood pressure exposures and cardiac structure outcomes defined above. We standardised all exposures and outcomes before analysis to have a mean of zero and SD of one. As such, all regression results are interpreted as the SD change in the outcome for a SD change in the exposure. For the binary dipping variables, the regression result can be interpreted as the change in outcome variable in SDs comparing the non-dippers category with the dippers.

Associations between each of the 18 BP exposures (for both SBP and DBP: clinic BP, 24h mean BP, mean daytime BP, mean night-time BP, SDdn, ARV, VIM and continuous and binary dipping variables) and 4 measures of cardiac structure (LVMi^2.7, LADi, RWT, LVIDD) were assessed using multivariable linear regression. Three models were estimated: i) adjustment for sex and age at year 17 clinic visit, ii) additional adjustment for potential confounders: maternal education, age at delivery, parity, pre-pregnancy BMI; household socio-economic class; smoking at age 17; minutes of moderate to vigorous physical activity at age 15; DXA-determined fat mass and height and height^2 at age 17, iii) further adjustment for average 24-hour blood pressure (systolic or diastolic as appropriate for the exposure) to evaluate whether any associations between BP variability and dipping were independent of 24-hour average BP.

To test for interactions between sex and each exposure, we regressed each outcome on each exposure, with sex and an interaction term for the exposure and sex as covariables. There was no strong evidence of any interactions by sex from these analyses (p>0.1 for all interaction terms), and as such, all results are presented for
males and females combined. We did not correct the results for multiple testing, as multiple testing correction emphasises the inappropriate dichotomisation of p values into significant versus non-significant \(^{32-35}\). Furthermore, in this analysis, exposures are correlated measures of a single underlying construct BP, and outcomes are measures of a single underlying construct, cardiac structure. A Bonferroni multiple testing correction would therefore be over-conservative. We interpret the overall pattern of results rather than focusing on single P values, and use the magnitude of coefficients and confidence intervals to assess the strength of associations.

**Missing Data**

Of the 587 participants with complete data on all 18 exposures and 4 outcomes, 196 (33.3\%) also had complete data including all confounders. In the full dataset, individual confounder variables were missing between 0\% and 43.4\% of observations, with eight of 11 variables having less than 13\% missingness (Supplementary Table 4). We used multivariate multiple imputation by chained equations to impute missing confounder data \(^{36,37}\). The imputation model included all exposures (excluding dipping variables, which were derived from other variables in the imputation model), outcomes and confounding variables, as well as weight and BMI at age 17, and maternal height. Fully conditional specification was used, with linear regression for continuous variables, multinomial regression for categorical variables and logistic regression for binary variables (Supplementary Table 4). We created twenty imputed datasets and used Rubin’s rules to combine analysis results. Variable distributions were consistent between the imputed and the observed data sets (Supplementary Table 4). We also conducted a complete case sensitivity analysis in the 196 participants with complete data for all variables (Supplementary Table 3).
Acknowledgements: We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. We also thank Kirsten Leyland for her analytical support.

Funding: The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. LJG is funded by a University of Bristol alumni PhD studentship as part of the British Heart Foundation 4-year Integrative Cardiovascular science programme. LDH is funded by a Career Development Award from the UK Medical Research Council (MR/M020894/1). LDH, SH, DAL and GDS work in a unit that receives funding from the University of Bristol and the UK Medical Research Council (MC_UU_00011/1 and MC_UU_00011/6-7). This grant was supported by a grant from the British Heart Foundation.

Disclosures: None.

References

1. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. May 2014;383(9932):1899-911.

doi:10.1016/S0140-6736(14)60685-1
2. Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. *Hypertens Res*. Jul 2012;35(7):695-701. doi:10.1038/hr.2012.26

3. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension*. Jan 2011;57(1):3-10. doi:10.1161/HYPERTENSIONAHA.109.133900

4. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens*. 01 2017;35(1):10-17. doi:10.1097/HJH.0000000000001159

5. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. Aug 2016;354:i4098.

6. de Swiet M, Fayers P, Shinebourne EA. Blood pressure in first 10 years of life: the Brompton study. *British Medical Journal*. 1/4/1992 1992;304(6818):23-26. Not in File.

7. McCarron P, Davey Smith G, Okasha M, McEwen J. Blood pressure in young adulthood and mortality from cardiovascular disease. *The Lancet*. 4/22/2000 2000;355(9213):1430-1431. Not in File. doi:doi: DOI: 10.1016/S0140-6736(00)02146-2

8. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. May 1990;322(22):1561-6. doi:10.1056/NEJM199005313222203
9. Armstrong AC, Liu K, Lewis CE, et al. Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: the CARDIA study. *Eur Heart J Cardiovasc Imaging*. Aug 2014;15(8):893-9. doi:10.1093/ehjci/jeu018

10. Mancusi C, Canciello G, Izzo R, et al. Left atrial dilatation: A target organ damage in young to middle-age hypertensive patients. The Campania Salute Network. *Int J Cardiol*. Aug 15 2018;265:229-233. doi:10.1016/j.ijcard.2018.03.120

11. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol*. Oct 2011;58(17):1733-40. doi:10.1016/j.jacc.2011.07.022

12. Wang S, Xue H, Zou Y, et al. Left ventricular hypertrophy, abnormal ventricular geometry and relative wall thickness are associated with increased risk of stroke in hypertensive patients among the Han Chinese. *Hypertens Res*. Sep 2014;37(9):870-4. doi:10.1038/hr.2014.88

13. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. *Stroke*. Oct 2003;34(10):2380-4. doi:10.1161/01.STR.0000089680.77236.60

14. Wade KH, Chiesa ST, Hughes AD, et al. Assessing the causal role of body mass index on cardiovascular health in young adults: Mendelian randomization and recall-by-genotype analyses. *Circulation*. 11 2018;138(20):2187-2201. doi:10.1161/CIRCULATIONAHA.117.033278

15. Sega R, Corrao G, Bombelli M, et al. Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension*. Feb 2002;39(2 Pt 2):710-4.
16. Zimpfer M, Vatner SF. Effects of acute increases in left ventricular preload on indices of myocardial function in conscious, unrestrained and intact, tranquilized baboons. *J Clin Invest.* Feb 1981;67(2):430-8. doi:10.1172/JCI110051

17. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J.* 06 2016;37(21):1642-50. doi:10.1093/eurheartj/ehv510

18. Boyd A, Golding J, Macleod J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol.* Feb 2013;42(1):111-27. doi:10.1093/ije/dys064

19. Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol.* Feb 2013;42(1):97-110. doi:10.1093/ije/dys066

20. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, Group GD. Management of hypertension: summary of NICE guidance. *BMJ.* Aug 2011;343:d4891. doi:10.1136/bmj.d4891

21. Anstey DE, Muntner P, Bello NA, et al. Diagnosing Masked Hypertension Using Ambulatory Blood Pressure Monitoring, Home Blood Pressure Monitoring, or Both? *Hypertension.* 11 2018;72(5):1200-1207. doi:10.1161/HYPERTENSIONAHA.118.11319

22. Bilo G, Giglio A, Styczkiewicz K, et al. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens.* Oct 2007;25(10):2058-66. doi:10.1097/HJH.0b013e32829c6a60

23. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens.* Mar 2005;23(3):505-11. doi:10.1097/01.hjh.0000160205.81652.5a
24. Hara A, Thijs L, Asayama K, Jacobs L, Wang JG, Staessen JA. Randomised double-blind comparison of placebo and active drugs for effects on risks associated with blood pressure variability in the Systolic Hypertension in Europe trial. PLoS One. 2014;9(8):e103169. doi:10.1371/journal.pone.0103169

25. Seeman T, Hradský O, Gilík J. Nocturnal blood pressure non-dipping is not associated with increased left ventricular mass index in hypertensive children without end-stage renal failure. Eur J Pediatr. Aug 2016;175(8):1091-7. doi:10.1007/s00431-016-2749-z

26. Salles GF, Reboldi G, Fagard RH, et al. Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) Meta-Analysis. Hypertension. Apr 2016;67(4):693-700. doi:10.1161/HYPERTENSIONAHA.115.06981

27. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol. Nov 1992;20(5):1251-60.

28. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. N Engl J Med. 04 2018;378(16):1509-1520. doi:10.1056/NEJMoa1712231

29. Howe LD, Lawlor DA, Propper C. Trajectories of socioeconomic inequalities in health, behaviours and academic achievement across childhood and adolescence. J Epidemiol Community Health. Apr 2013;67(4):358-64. doi:10.1136/jech-2012-201892

30. Laitinen TT, Puolakka E, Ruohonen S, et al. Association of Socioeconomic Status in Childhood With Left Ventricular Structure and Diastolic Function in
Adulthood: The Cardiovascular Risk in Young Finns Study. *JAMA Pediatr.* 08 2017;171(8):781-787. doi:10.1001/jamapediatrics.2017.1085

31. Harville EW, Apolzan JW, Bazzano LA. Maternal Pre-Pregnancy Cardiovascular Risk Factors and Offspring and Grandoffspring Health: Bogalusa Daughters. *Int J Environ Res Public Health.* 12 2018;16(1)doi:10.3390/ijerph16010015

32. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? *BMJ.* Jan 2001;322(7280):226-31. doi:10.1136/bmj.322.7280.226

33. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature.* 03 2019;567(7748):305-307. doi:10.1038/d41586-019-00857-9

34. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ.* Apr 1998;316(7139):1236-8. doi:10.1136/bmj.316.7139.1236

35. Harrington D, D'Agostino RB, Gatsonis C, et al. New Guidelines for Statistical Reporting in the. *N Engl J Med.* 07 2019;381(3):285-286. doi:10.1056/NEJMe1906559

36. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* Feb 2011;30(4):377-99. doi:10.1002/sim.4067

37. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med.* Dec 2010;29(28):2920-31. doi:10.1002/sim.3944

38. Muntner P, Shimbo D, Diaz KM, Newman J, Sloan RP, Schwartz JE. Low correlation between visit-to-visit variability and 24-h variability of blood pressure. *Hypertens Res.* Nov 2013;36(11):940-6. doi:10.1038/hr.2013.58
39. Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. *Hypertens Res*. Mar 2016;39(3):171-7. doi:10.1038/hr.2015.126

40. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. Mar 2010;375(9718):895-905. doi:10.1016/S0140-6736(10)60308-X

41. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension*. Apr 2010;55(4):1049-57. doi:10.1161/HYPERTENSIONAHA.109.140798

42. Chen W, Srinivasan SR, Ruan L, Mei H, Berenson GS. Adult hypertension is associated with blood pressure variability in childhood in blacks and whites: the bogalusa heart study. *Am J Hypertens*. Jan 2011;24(1):77-82. doi:10.1038/ajh.2010.176

43. Bjelakovic B, Lukic S, Vukomanovic V, et al. Blood pressure variability and left ventricular mass index in children. *J Clin Hypertens (Greenwich)*. Dec 2013;15(12):905-9. doi:10.1111/jch.12206

44. Leisman D, Meyers M, Schnall J, et al. Blood pressure variability in children with primary vs secondary hypertension. *J Clin Hypertens (Greenwich)*. Jun 2014;16(6):437-41. doi:10.1111/jch.12322

45. Belsha CW, Wells TG, McNiece KL, Seib PM, Plummer JK, Berry PL. Influence of diurnal blood pressure variations on target organ abnormalities in adolescents with mild essential hypertension. *Am J Hypertens*. Apr 1998;11(4 Pt 1):410-7.
46. Lee H, Kong YH, Kim KH, Huh J, Kang IS, Song J. Left ventricular hypertrophy and diastolic function in children and adolescents with essential hypertension. *Clin Hypertens.* 2015;21:21. doi:10.1186/s40885-015-0031-8

47. Picone DS, Schultz MG, Otahal P, et al. Accuracy of Cuff-Measured Blood Pressure: Systematic Reviews and Meta-Analyses. *J Am Coll Cardiol.* Aug 2017;70(5):572-586. doi:10.1016/j.jacc.2017.05.064

48. Fagard R, Staessen JA, Thijs L. The relationships between left ventricular mass and daytime and night-time blood pressures: a meta-analysis of comparative studies. *J Hypertens.* Aug 1995;13(8):823-9. doi:10.1097/00004872-199508000-00002

49. Woodiwiss AJ, Libhaber CD, Sareli P, Norton GR. Impact of Blunted Nocturnal Blood Pressure Dipping on Cardiac Systolic Function in Community Participants Not Receiving Antihypertensive Therapy. *Am J Hypertens.* 08 2018;31(9):1002-1012. doi:10.1093/ajh/hpy075

50. Bello NA, Jaeger BC, Booth JN, et al. Associations of awake and asleep blood pressure and blood pressure dipping with abnormalities of cardiac structure: the Coronary Artery Risk Development in Young Adults study. *J Hypertens.* 01 2020;38(1):102-110. doi:10.1097/HJH.0000000000002221

51. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology.* Jul 2006;17(4):413-8. doi:10.1097/ede.0000220549.14177.60

52. Henskens LH, van Boxtel MP, Kroon AA, van Oostenbrugge RJ, Lodder J, de Leeuw PW. Subjective sleep disturbance increases the nocturnal blood pressure level and attenuates the correlation with target-organ damage. *J Hypertens.* Feb 2011;29(2):242-50.
Tables

Table 1. Measures of blood pressure and cardiac structure for participants included in the analysis, N=587

| Variable                      | Combined mean (SD) or frequency (%) N=587 | Mean (SD) or frequency (%) in males N=253 | Mean (SD) or frequency (%) in females N=334 | P value for sex difference |
|-------------------------------|-------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------|
| **Systolic Blood Pressure**   |                                           |                                           |                                            |                           |
| Clinic SBP (mmHg)             | 114.5 (9.7)                               | 119.7 (8.9)                               | 110.5 (8.3)                                | <0.001                    |
| 24h average SBP (mmHg)        | 118.3 (8.6)                               | 121.4 (7.7)                               | 115.9 (8.4)                                | <0.001                    |
| Daytime average SBP (mmHg)    | 124.8 (9.2)                               | 128.3 (8.5)                               | 122.1 (8.8)                                | <0.001                    |
| Night time average SBP (mmHg) | 107.4 (9.2)                               | 109.8 (8.9)                               | 105.6 (9.0)                                | 0.001                     |
| SDdn SBP (mmHg)               | 10.2 (2.1)                                | 10.6 (2.1)                                | 9.9 (2.1)                                  | <0.001                    |
| VIM of SBP (mmHg)             | 10.2 (2.0)                                | 10.3 (1.9)                                | 10.1 (1.7)                                 | P=0.14                    |
| ARV of SBP (mmHg)             | 10.5 (2.5)                                | 10.9 (2.5)                                | 10.1 (2.5)                                 | <0.001                    |
| Systolic dipping (%)          | 13.8 (5.7)                                | 14.4 (5.8)                                | 13.4 (5.5)                                 | 0.05                      |
| Binary systolic dipping:                      |                  |                  |                  | 0.20*          |
|---------------------------------------------|------------------|------------------|------------------|---------------|
| - Dippers (>10%)                            | 456 (77.7 %)     | 203 (80.2 %)     | 253 (75.8 %)     |               |
| - Non-dippers (≤10%)                         | 131 (22.3 %)     | 50 (19.8 %)      | 81 (24.3 %)      |               |
| Categorical systolic dipping:                |                  |                  |                  | 0.11          |
| - Normal dippers (>10%, ≤20%)               | 216 (64.7%)      | 160 (63.2 %)     | 216 (64.7 %)     |               |
| - Non-dippers (0-10%)                        | 78 (23.4%)       | 46 (18.2 %)      | 78 (23.4 %)      |               |
| - Extreme dippers (>20%)                    | 37 (11.1%)       | 43 (17.1 %)      | 37 (11.1 %)      |               |
| - Risers (<0%)                              | 3 (0.9%)         | 4 (1.7 %)        | 3 (0.9 %)        |               |

**Diastolic Blood Pressure**

|                          |                  |                  |                  |               |
|--------------------------|------------------|------------------|------------------|---------------|
| Clinic DBP (mmHg)        | 64.5 (5.8)       | 63.3 (5.3)       | 65.4 (6.1)       | <0.001        |
| 24h mean DBP (mmHg)      | 67.9 (5.2)       | 67.5 (5.1)       | 68.1 (5.3)       | 0.15          |
| Daytime average DBP (mmHg)| 73.5 (5.9)      | 73.1 (5.9)       | 73.9 (5.9)       | 0.13          |
| Night time average DBP (mmHg)| 58.3 (5.5)   | 57.9 (5.3)       | 58.7 (5.6)       | 0.07          |
| SDdn DBP (mmHg)          | 8.4 (1.8)        | 8.7 (1.9)        | 8.2 (1.7)        | 0.001         |
| VIM of DBP (mmHg)        | 8.4 (1.8)        | 8.8 (1.9)        | 8.1 (1.7)        | <0.001        |
|                        | Group 1       | Group 2       | Group 3       | p-value |
|------------------------|---------------|---------------|---------------|---------|
| ARV of DBP (mmHg)      | 8.8 (2.0)     | 9.1 (2.1)     | 8.6 (1.9)     | 0.005   |
| Diastolic dipping (%)  | 20.5 (6.9)    | 20.7 (6.8)    | 20.4 (7.0)    | 0.59    |
| Binary diastolic dipping: |              |               |              | 0.99*   |
| - Dippers (>10%)       | 550 (93.7 %)  | 237 (93.7 %)  | 313 (93.7 %)  |         |
| - Non-dippers (≤10%)   | 37 (6.3 %)    | 16 (6.3 %)    | 21 (6.3 %)    |         |
| Categorical diastolic dipping: |             |               |              | 0.91    |
| - Normal dippers (>10%, ≤20%) | 218 (37.1 %) | 91 (36.0 %)   | 127 (38.2 %)  |         |
| - Non-dippers (0-10%)  | 31 (5.3 %)    | 14 (5.5 %)    | 17 (5.1 %)    |         |
| - Extreme dippers (>20%) | 332 (56.6 %) | 146 (57.7 %)  | 186 (55.7 %)  |         |
| - Risers (<0%)         | 6 (1.0 %)     | 2 (0.8 %)     | 4 (1.2 %)     |         |

**Cardiac structure measures**

|                        | Group 1       | Group 2       | Group 3       | p-value |
|------------------------|---------------|---------------|---------------|---------|
| LVMi (g/m$^2$.7)       | 27.7 (5.9)    | 29.3 (6.2)    | 26.5 (5.4)    | <0.001  |
| LADi (cm/m)            | 1.88 (0.22)   | 1.87 (0.23)   | 1.88 (0.22)   | 0.42    |
| LVIDD (cm)             | 4.52 (0.44)   | 4.76 (0.41)   | 4.33 (0.36)   | <0.001  |
| RWT                    | 0.37 (0.06)   | 0.37 (0.05)   | 0.37 (0.06)   | 0.92    |
* = using Pearson's Chi-Squared test for the categorical dipping variable; SBP = systolic blood pressure, SDdn = standard deviation weighted for day and night, ARV = average real variability, VIM = variability independent of the mean, DBP = diastolic blood pressure, LVMi$^{2.7}$ = left ventricular mass indexed to height$^{2.7}$, LADI = left atrial diameter indexed to height, LVIDD = left ventricular internal diameter during diastole, RWT = relative wall thickness.
Table 2. Associations of blood pressure measurements with cardiac structure, N=587

Analysis of multiply imputed data. Adjusted for sex, age at outcome assessment; maternal age at delivery, education, parity, and maternal pre-pregnancy BMI; household social class; smoking at age 17; minutes of moderate to vigorous physical activity at age 15; DXA-determined fat mass, height and height² at age 17. Regression coefficients for continuous exposures are standardised, i.e. they represent the change in SDs of the outcome (cardiac structure measurement) per one SD higher blood pressure.

| Exposure              | Mean difference in cardiac structure measures (SDs) per SD higher BP: β, 95% confidence interval, P value |
|-----------------------|----------------------------------------------------------------------------------------------------------|
|                       | LVMi                                           | LADi                                    | LVIDD                                | RWT                                     |
| SBP                   | 0.23 (0.15 to 0.32)                              | 0.055 (-0.039 to 0.15)                  | -0.0043 (-0.085 to 0.077)             | 0.29 (0.19 to 0.39)                     |
|                       | P=1.6x10⁻⁷                                      | P=0.25                                  | P=0.92                               | P=1.2x10⁻⁸                             |
| 24h mean SBP          | 0.17 (0.093 to 0.25)                             | -0.006 (-0.088 to 0.076)                | 0.016 (-0.056 to 0.087)               | 0.18 (0.089 to 0.26)                    |
|                       | P=1.8x10⁻⁵                                      | P=0.89                                  | P=0.67                               | P=8.1x10⁻⁵                             |
| Daytime mean SBP      | 0.17                                            | 0.018                                   | 0.026                                | 0.16                                   |
|                  | Lower Bound     | Upper Bound     | P Value          | Lower Bound     | Upper Bound     | P Value          |
|------------------|-----------------|-----------------|------------------|-----------------|-----------------|------------------|
| **Night-time mean SBP** | (0.097 to 0.25) | -0.065 to 0.10  | (0.073 to 0.25)  | 1.2x10^-5       | 0.68            | 3.5x10^-4        |
|                  | 0.042 to 0.19   | -0.096 to 0.064 |                  | 2.3x10^-3       | 0.70            |                  |
|                  | 0.016           | -0.025          | 0.18             |                 |                 |                  |
|                  | -0.046 to 0.098 |                  |                  |                 |                 |                  |
| **SDdn SBP**     | 0.073           | -0.003 to 0.15  | 0.15             | 0.073           | -0.003 to 0.15  | 0.060            |
|                  | (-0.003 to 0.15)|                  |                  |                 |                 |                  |
|                  | 0.019           | -0.088 to 0.050 |                  |                 |                 |                  |
|                  | 0.060           | -0.060 to 0.098 |                  |                 |                 |                  |
|                  | 0.019           |                  |                  |                 |                 |                  |
| **VIM of SBP**   | 0.018           | -0.058 to 0.093 | 0.087            | 0.018           | -0.058 to 0.093 | 0.065            |
|                  | (-0.058 to 0.093)|                  |                  |                 |                 |                  |
|                  | 0.031           | -0.091 to 0.047 |                  |                 |                 |                  |
|                  | (-0.047 to 0.11)|                  |                  |                 |                 |                  |
|                  | -0.022          |                  |                  |                 |                 |                  |
| **ARV of SBP**   | 0.091           | -0.012 to 0.14  | 0.12             | 0.091           | -0.012 to 0.14  | 0.017            |
|                  | (0.016 to 0.17) |                  |                  |                 |                 |                  |
|                  | 0.067           | -0.058 to 0.078 |                  |                 |                 |                  |
|                  | (-0.012 to 0.14)|                  |                  |                 |                 |                  |
|                  | 0.010           |                  |                  |                 |                 |                  |
|                  | (-0.058 to 0.078)|                  |                  |                 |                 |                  |
|                  | 0.12            |                  |                  |                 |                 |                  |
|                  | (0.039 to 0.21) |                  |                  |                 |                 |                  |
| Systolic dipping          | 0.033 (-0.043 to 0.11) | 0.038 (-0.042 to 0.12) | 0.060 (-0.010 to 0.13) | -0.069 (-0.15 to 0.017) |
|--------------------------|------------------------|------------------------|------------------------|------------------------|
| (continuous)             | P=0.39                 | P=0.35                 | P=0.09                 | P=0.12                 |
| Binary systolic dipping  | -0.10 (-0.28 to 0.080) | -0.073 (-0.26 to 0.12) | -0.039 (-0.20 to 0.13) | -0.0005 (-0.20 to 0.20) |
| (non-dippers versus      |                        |                        |                        |                        |
| dippers)                 |                        |                        |                        |                        |
| DBP                      | 0.034 (-0.046 to 0.11) | -0.10 (-0.19 to -0.015)| -0.13 (-0.20 to -0.055)| 0.24 (0.15 to 0.33)    |
|                          | P=0.41                 | P=0.021                | P=5.7x10^{-4}          | P=1.4x10^{-7}          |
| 24h mean DBP             | 0.050 (-0.024 to 0.12) | -0.075 (-0.15 to 0.0006)| -0.055 (-0.12 to 0.013)| 0.13 (0.045 to 0.21)   |
|                          | P=0.18                 | P=0.052                | P=0.11                 | P=2.6x10^{-3}          |
| Daytime mean DBP         | 0.059 (-0.015 to 0.1)  | -0.046 (-0.12 to 0.032)| -0.053 (-0.12 to 0.015)| 0.14 (0.052 to 0.22)   |
|                          | P=0.12                 | P=0.24                 | P=0.12                 | P=1.5x10^{-3}          |
| Variable                        | Value 1        | Value 2        | Value 3        | Value 4        |
|--------------------------------|----------------|----------------|----------------|----------------|
| Night-time mean DBP            | 0.021          | -0.081         | -0.074         | 0.13           |
|                               | (-0.053 to 0.094) | (-0.16 to -0.003) | (-0.14 to -0.007) | (0.044 to 0.21) |
|                               | P=0.58         | P=0.042        | P=0.03         | P=2.8x10^-3    |
| SDdn DBP                       | 0.073          | 0.064          | -0.022         | 0.15           |
|                               | (-0.002 to 0.15) | (-0.014 to 0.14) | (-0.090 to 0.047) | (0.062 to 0.23) |
|                               | P=0.056        | P=0.11         | P=0.54         | P=7.2x10^-4    |
| VIM of DBP                     | 0.064          | 0.10           | 0.010          | 0.090          |
|                               | (-0.012 to 0.14) | (0.025 to 0.18) | (-0.060 to 0.080) | (0.0045 to 0.18) |
|                               | P=0.098        | P=9.8x10^-3    | P=0.77         | P=0.039        |
| ARV of DBP                     | 0.083          | 0.11           | -0.009         | 0.13           |
|                               | (0.008 to 0.16) | (0.036 to 0.19) | (-0.078 to 0.060) | (0.045 to 0.21) |
|                               | P=0.030        | P=4.3x10^-3    | P=0.80         | P=2.7x10^-3    |
| Diastolic dipping (continuous) | 0.032          | 0.047          | 0.032          | -0.014         |
|                               | (-0.043 to 0.11) | (-0.031 to 0.13) | (-0.037 to 0.10) | (-0.10 to 0.071) |
|                               | P=0.40         | P=0.24         | P=0.36         | P=0.74         |
| Binary diastolic dipping (non-dippers versus dippers) | -0.22 (-0.52 to 0.084) | -0.21 (-0.52 to 0.11) | -0.15 (-0.43 to 0.13) | -0.037 (-0.38 to 0.31) |
|-----------------------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                                                     | P=0.16                | P=0.20                | P=0.28                | P=0.83                |

LVMi = left ventricular mass indexed to height\(^2\), LADi = left atrial diameter indexed to height, LVIDD = left ventricular internal diameter during diastole, RWT = relative wall thickness. SBP = systolic blood pressure, SDdn = standard deviation weighted for day and night, VIM = variability independent of the mean, ARV = average real variability, DBP = diastolic blood pressure.
Table 3. Associations of BP variability and dipping with cardiac structure after adjustment for 24-hour mean BP, N=587

Analysis of multiply imputed data. Adjusted for sex, age at outcome assessment; maternal age at delivery, education, parity, and maternal pre-pregnancy BMI; household social class; smoking at age 17; minutes of moderate to vigorous physical activity at age 15; DXA-determined fat mass, height and height$^2$ at age 17; mean 24-hour blood pressure (systolic or diastolic, as appropriate for the exposure). Regression coefficients are standardised, i.e. they represent the change in SDs of the outcome (cardiac structure measurement) per one SD higher blood pressure.

| Exposure      | Mean difference in cardiac structure measures (SDs) per SD higher BP: $\beta$, 95% confidence interval, P value |       |       |       |
|---------------|----------------------------------------------------------------------------------------------------------------|-------|-------|-------|
|               | LVMi                                                                                                           | LADI  | LVIDD | RWT   |
| SDdn SBP      | 0.020                                                            (-0.059 to 0.099)                      | 0.024 (-0.060 to 0.11)                      | -0.027 (-0.10 to 0.046)                     | 0.10 (0.011 to 0.19)                        |
|               | (P=0.62)                                                         (P=0.58)                                    | (P=0.47)                                    | (P=0.028)                                   |
| VIM of SBP    | 0.020                                                            (-0.054 to 0.094)                      | 0.031 (-0.048 to 0.11)                      | -0.022 (-0.091 to 0.047)                    | 0.090 (0.0054 to 0.17)                      |
|               | (P=0.59)                                                         (P=0.44)                                    | (P=0.53)                                    | (P=0.037)                                   |
|                              | ARV of SBP | Systolic dipping (continuous) | Binary systolic dipping (non-dippers versus dippers) | SDdn DBP | VIM of DBP |
|------------------------------|------------|-------------------------------|------------------------------------------------|---------|-----------|
|                              | 0.044      | 0.038                         | -0.14                                         | 0.066   | 0.076     |
|                              | (-0.034 to 0.12) | (-0.042 to 0.12) | (-0.31 to 0.041) | (-0.01 to 0.14) | (-0.0007 to 0.15) |
|                              | P=0.27     | P=0.35                        | P=0.13                                        | P=0.089 | P=0.052   |
|                              |            |                               |                                               | 0.081   | 0.093     |
|                              |            |                               |                                               | (0.0013 to 0.16) | (0.012 to 0.17) |
|                              |            |                               |                                               | P=0.046 | P=0.024   |
|                              |            |                               |                                               | P=0.12  | -0.0002   |
|                              |            |                               |                                               | (0.082 to 0.058) | (-0.071 to 0.070) |
|                              |            |                               |                                               | P=0.74  | 0.12      |
|                              |            |                               |                                               | P=3.7x10^{-3} | (0.033 to 0.20) |
|                              |            |                               |                                               | P=0.99  | P=6.9x10^{-3} |
|                          | ARV of DBP       | Diastolic dipping (continuous) | Binary diastolic dipping (non-dippers versus dippers) |
|--------------------------|------------------|--------------------------------|-----------------------------------------------------|
|                          | 0.076            | 0.031                          | -0.24                                               |
|                          | (-0.0007 to 0.15)| (-0.044 to 0.11)               | (-0.54 to 0.068)                                    |
|                          | P=0.052          | P=0.42                         | P=0.13                                              |
|                          | 0.14             | 0.050                          | -0.18                                               |
|                          | (0.055 to 0.21)  | (-0.028 to 0.13)               | (-0.50 to 0.13)                                    |
|                          | P=9.2x10^{-4}    | P=0.21                         | P=0.25                                              |
|                          | 0.0021           | 0.034                          | -0.14                                               |
|                          | (-0.068 to 0.072)| (-0.034 to 0.10)               | (-0.4 to 0.14)                                     |
|                          | P=0.95           | P=0.33                         | P=0.33                                              |
|                          | 0.11             | -0.020                         | -0.076                                              |
|                          | (0.022 to 0.19)  | (-0.10 to 0.065)               | (-0.42 to 0.27)                                    |
|                          | P=0.014          | P=0.65                         | P=0.66                                              |

LVMi = left ventricular mass indexed to height, LADi = left atrial diameter indexed to height, LVIDD = left ventricular internal diameter during diastole, RWT = relative wall thickness. SBP = systolic blood pressure, DBP = diastolic blood pressure, SDdn = standard deviation weighted for day and night, VIM = variability independent of the mean, ARV = average real variability.
**Figures**

**Figure 1**

Figure 1: a STROBE diagram detailing how the study cohort was selected from the baseline Avon Longitudinal Study of Parents And Children (ALSPAC) participants.
Figure 2: Forest plot of the mean difference in left ventricular mass indexed to height (LVMi) in SDs +/- 95% confidence interval per SD higher blood pressure variable in the confounder model. SDdn = Standard deviation weighted for day and night, VIM = variability independent of the mean, ARV = average real variability.