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Inter-arm difference and cardiovascular risk estimation in primary care
(Running title: Inter-arm difference and cardiovascular risk in primary care)

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Abstract

Background
Systolic inter-arm differences (IAD) in blood pressure (BP) contribute independently to cardiovascular risk estimates; this can be used to refine predicted risk and guide personalised interventions.

Aim
To model the effect of accounting for IAD in cardiovascular risk estimation in a primary care population free of pre-existing cardiovascular disease.

Design and setting
Cross-sectional analysis of people aged 40-75 years attending National Health Service (NHS) Health Checks in one general practice in England.

Method
Simultaneous bilateral BP measurements were made during Health Checks. QRISK2, ASCVD and Framingham cardiovascular risk scores were calculated before and after adjustment for IAD using previously published hazard ratios. Reclassification across guideline-recommended intervention thresholds was analysed.

Results
Data for 334 participants were analysed. Mean (standard deviation) QRISK2, ASCVD and Framingham scores were 8.0 (6.9), 6.9 (6.5) and 10.7 (8.1) respectively rising to 8.9 (7.7), 7.1 (6.7) and 11.2 (8.5) after adjustment for IAD. 13 (3.9%) participants were reclassified from below to above the 10% QRISK2 threshold, 3 (0.9%) for the ASCVD 10% threshold and 9 (2.7%) for the Framingham 15% threshold.

Conclusion
Knowledge of IAD can be used to refine cardiovascular risk estimates in primary care. By accounting for IAD, recommendations of interventions for primary prevention of cardiovascular disease can be personalised and treatment offered to those at greater than average risk. When assessing elevated clinic BP readings, both arms should be measured to allow fuller estimation of cardiovascular risk.

Key words: blood pressure determination, hypertension, cardiovascular risk factors, primary health care, screening
How this fits in
Systolic inter-arm blood pressure differences (IAD) are independently associated with increased risks of all-cause mortality, cardiovascular mortality and cardiovascular events.

How cardiovascular risk can best be assessed taking IAD into account has not been demonstrated.

This study applies robust estimates of the additional cardiovascular risk associated with an IAD to a primary care population free of existing vascular disease.

The effect of an IAD on reclassification of individuals across commonly used cardiovascular risk intervention thresholds, to refine estimates of risk and personalise treatment decisions, is demonstrated.
Introduction
Cardiovascular disease is the primary cause of premature morbidity and mortality across the globe, and high blood pressure (BP) is a leading contributor to cardiovascular events. Optimising management of hypertension is therefore recommended by the UK Quality and Outcomes Framework (QOF) for the prevention of cardiovascular disease, and in primary care settings BP measurement is the most frequently undertaken investigation.

Typically, individuals with the highest estimated cardiovascular risk reap the most benefit from antihypertensive treatment, but the overall majority of cardiovascular events occur in those at low to medium risk. Assessment of ten-year cardiovascular risk using established risk scores is a common recommendation of international hypertension guidelines. In the UK risk assessment for primary prevention of cardiovascular disease is advised by the National Institute of Health and Care excellence (NICE) using QRISK scores. Similarly the American College of Cardiology/American Heart Association (ACA/AHA) uses Atherosclerotic Cardiovascular Disease (ASCVD) risk scores based on the ACA/AHA Pooled Cohort Equations, and Hypertension Canada uses the Framingham risk score. Risk scores exceeding defined thresholds are used to guide initiation or intensification of treatment, usually by addition of antihypertensive agents and/or statins. Not all markers of cardiovascular risk identified within guidelines are captured by currently used risk scores. Consideration of such additional markers, indicating possible subclinical arterial disease, could serve to refine and improve selection of people at risk greater than their peers who may, therefore, benefit from more intensive intervention.

Some recognised risk markers for refining intermediate cardiovascular risk, such as assessment of coronary artery calcium require significant technological investment. Since primary prevention takes place in primary care, any practical identification of additional risk markers should be low cost and feasible for widespread implementation. Measurement of BP in both arms can feasibly be incorporated into routine primary care without needing additional equipment. It is recommended
internationally in guidelines, to accurately assess BP and to determine the higher reading arm for subsequent BP measurement and management. These guidelines also highlight the association of inter-arm differences (IAD) in systolic BP with additional cardiovascular risk.\textsuperscript{5,8,10,15} Despite guideline advice to measure both arms when assessing people for hypertension, this may only be applied in 50% of settings at best.\textsuperscript{16}

General Practitioner awareness of guideline recommendations is higher than implementation; it has been suggested that presenting clear evidence and justification for recommendations could increase adoption in practice.\textsuperscript{17,18} We have recently reported findings from the large inter-arm BP difference individual participant data (INTERPRESS-IPD) Collaboration which pooled data from over 53,000 individuals with BP measured in both arms from 24 international cohorts. We confirmed the independent contribution of systolic IAD to cardiovascular risk, developed and validated risk prediction models that incorporated IAD measurement. We also confirmed and quantified the association of IAD with elevated risk after adjustment for ASCVD, Framingham or QRISK2 risk scores, providing data that can be directly applied to a primary care population.\textsuperscript{19}

The Department of Health (DoH) introduced the National Health Service (NHS) Health Check Programme in 2009; it invites individuals aged 40 to 74 years, who are free of cardiovascular disease, to attend a cardiovascular assessment session, usually in primary care practices, every five years.\textsuperscript{20} This session includes BP measurements and other risk marker assessments, thus offering the opportunity to measure BP in both arms to identify IAD in people without a vascular disease diagnosis. The impact of taking account of IAD during cardiovascular risk assessment in a primary care population free of cardiovascular disease has not been demonstrated. Therefore, this pilot study was undertaken to model the application of our adjustments to existing cardiovascular risk scores, taking account of systolic IAD, in a new cohort (not included in the INTERPRESS-IPD Collaboration) presenting to one general practice for routine NHS Health Checks.\textsuperscript{19}
Methods
This analysis was undertaken using data collected during the Check-Up study programme.21 22

Participants
From October 2013, patients aged 40 to 74 years, registered with the Mid Devon Medical Practice (a rural dispensing practice, list size 5000 across three sites in Devon, England), and not already included in any existing vascular disease register, were identified from practice records and invited by letter to book in to a nurse-led NHS Health Check assessment.23 Patients with pre-existing hypertension, atrial fibrillation (AF), chronic kidney disease, stroke or transient ischaemic attack, heart disease, diabetes or peripheral arterial disease were excluded.

Patients underwent an NHS Health Check assessment which included targeted brief health interventions based on lifestyle, history and clinical measurements, and blood sampling. BP was measured using an automated sphygmomanometer (Microlife Watch BP Office, Microlife AG, Switzerland) after five minutes of seated rest. This two-cuff device measures three consecutive readings taken one minute apart, simultaneously in both arms, and reports the mean of three readings for each arm. Irregular pulse is also reported; diagnostic electrocardiograms (ECGs) were performed when an irregular pulse was flagged by the device (Supplementary Figure S1).

Patients were referred for ambulatory blood pressure monitoring if a diagnosis of hypertension was suspected from a clinic reading >140/90 mmHg, and for repeat blood tests if diabetes or chronic kidney disease (CKD) were suspected based on the initial investigations (Supplementary Figure S1).

All patients attending the Health Check received a follow-up letter summarising their results, including a QRISK2 10-year cardiovascular risk assessment score and lifestyle recommendations. Information on dementia was also supplied to those aged over 65 years.

This was a pilot study, undertaken to model application of our adjustments to cardiovascular risk scores, in a single practice cohort with documented IAD, therefore no formal sample size estimates were calculated.
Analysis
Health Check data were collated prospectively in an Excel spreadsheet (Microsoft Corp, Redmond, Washington, USA) and analysed using Stata v17.0 (Statacorp, Texas, USA). Descriptive data were summarised as means and standard deviations or proportions as appropriate. QRISK2 scores were calculated online as part of the Health Check process; Framingham and ASCVD risk scores were calculated in Stata using published algorithms. The higher reading systolic arm BP was used in all cardiovascular risk calculations. Cardiovascular risk scores were adjusted to take account of measured IAD, by applying hazard ratios derived from our INTERPRESS-IPD Collaboration (Supplementary Figures S2 to S4). Reclassification across key international hypertension guideline thresholds for intervention according to estimated cardiovascular risk (NICE 2019 – QRISK2 10%; ACC/AHA – ASCVD 10%; Hypertension Canada – Framingham 15%) was calculated by comparing risk scores before and after adjustment of scores for IAD. Data analysis was restricted to participants attending and completing Health Checks; no imputations of missing data were undertaken.
Results
1800 patients (36% of registered list) were eligible for invitation to complete an NHS Health Check assessment over the succeeding five years from October 2013. Between November 2013 and December 2015; 636 (35%) patients were invited; 340 attended of whom 334 (53%; 95% confidence interval (CI) 50% to 57%) attended and completed a Health Check appointment with full data capture. Mean (standard deviation) age of participants was 57.4 (9.3) years, 58% were female and mean systolic/diastolic BP was 132 (14)/79 (8.5) mmHg (Table 1). After appropriate follow-up investigations, new diagnoses of hypertension were confirmed in 13 (3.9%) attenders, type 2 diabetes mellitus in five (1.5%) and CKD stage 3 in five (1.5%; Figure 1). Of five (1.5%) participants identified as having an irregular pulse by the Watch BP Office device; none were confirmed to have AF on 12-lead ECGs. Overall, 31 (9.3%) participants had a systolic IAD $\geq$ 10 mmHg and 10 (3%) a diastolic IAD $\geq$ 10 mmHg at the Health Check appointment (Figure 2).

Ten-year risks of cardiovascular events, when adjusted for IAD risk, were significantly higher for QRISK2, ASCVD and Framingham risk scores ($P < 0.001$ for all scores; Table 2; Figure 3). By adjusting cardiovascular risk scores to take account of systolic IAD, 13 (3.9%) participants were reclassified from below to above a 10% QRISK2-based treatment threshold; three participants (0.9%) were reclassified from below to above the 10% ASCVD treatment threshold. These represent 13/35 (37%) of participants presenting with an unadjusted QRISK2 between 8% and 9.9%, and 3/29 (10.3%) with an unadjusted ASCVD risk of 8% to 9.9%. For the Framingham 15% intervention threshold, nine (2.7%) were reclassified from below to above the threshold, representing 9/38 (23.7%) of participants with an unadjusted Framingham score between 12% and 14.9% (Table 2; Figure 3).
Discussion

Summary

This pilot study demonstrates that BP can be measured in both arms to determine IAD during routine NHS Health Check assessments. Adjustment of QRISK2 estimated cardiovascular risk to account for IAD reclassified 4% of participants from below to above the NICE QRISK2 intervention threshold. Similar effects were seen when IAD was used to adjust other cardiovascular risk scores. These adjustments are most relevant to those participants with risk scores below but close to intervention thresholds, where adjustment for IAD had a proportionally larger effect on reclassification across risk categories.

These pilot findings show that cardiovascular risk classification can usefully be refined, by measuring BP in both arms and taking account of the inter-arm difference, during NHS Health Checks.

Strengths and limitations

Systematic data collection throughout the Health Check process achieved low levels of missing data.

When compared to attenders, non-attenders in this study had twice the smoking rate and significantly higher BP readings in previous primary care records. Attendance at NHS Health Checks is associated with more positive and pro-active attitudes toward personal healthcare; lower attendance is also observed from people living with higher levels of deprivation. For these reasons the mean cardiovascular risk for the cohort studied here is likely to be lower than that for the full eligible practice population. These findings are derived from a single rural practice in Devon with low ethnic diversity. Cardiovascular risk varies with ethnicity, but we have previously shown no variation of IAD in England according to ethnic origin. Nevertheless, we are cautious of attempting to generalise our findings to a wider primary care population. The results of this pilot study do, however, illustrate the practical application of our published risk tables (available at: https://medicine.exeter.ac.uk/research/healthresearch/primarycare/interpress-ipd/riskadjustmenttables/) in a primary care setting, indicating the potential use of IAD to refine cardiovascular risk assessment. The hazard ratios applied to IAD are derived from our separate
INTERPRESS-IPD Collaboration; the largest international dataset assembled to examine the implications of an IAD for prediction of mortality and cardiovascular mortality.\textsuperscript{19}

This study used the Microlife Watch BP Office device – a two cuff device capable of repeated simultaneous measures with good reproducibility.\textsuperscript{26} Our INTERPRESS-IPD Collaboration data are derived largely from sequential BP measurements, which generally yield a greater magnitude in IAD than comparable simultaneous measurements.\textsuperscript{27,28} Consequently this analysis may have produced estimates of the proportions reclassified by taking account of IAD that are conservative in comparison to sequential assessment of BP in routine practice.

Comparison with existing literature
Arterial stiffening is an early indicator of hypertension-mediated organ damage such as left ventricular hypertrophy – an important marker of adverse prognosis.\textsuperscript{29} Its presence is suggested in people over 60 years by a widening pulse pressure (systolic minus diastolic BP >60 mmHg) or at any age by an elevated pulse-wave velocity (PWV).\textsuperscript{30} Whilst pulse pressure is easily calculated, measurement of PWV is not practical in routine primary care. There is good evidence to support the association of systolic IAD with increased arterial stiffness; it is correlated with increased PWV and left ventricular wall thickening.\textsuperscript{31-33} Both arterial stiffness and IAD are associated prospectively with higher rates of cardiovascular events, cardiovascular mortality and all-cause mortality.\textsuperscript{15,19,34} A systolic IAD has an independent prognostic value for mortality and cardiovascular events over and above that predicted by established risk scores, which we believe is explained by its value as a non-invasive indicator of subclinical arterial disease.\textsuperscript{31,19} The current analyses apply our estimates of the impact of systolic IAD on cardiovascular risk scores in a pilot study. They demonstrate the likely impact of assessing an IAD on workload, by refining and increasing the proportions attending an NHS Health Check who will require further investigation for diagnosis and potentially management of hypertension and/or elevated cardiovascular risk.
Implications for research and/or practice
In the absence of pre-existing vascular disease, intervention with statin and/or BP lowering treatment is guided by individual assessment of cardiovascular risk. Our pilot findings confirm that a systolic IAD can be applied to refine cardiovascular risk estimates in a UK single primary care population. By taking account of systolic IAD, decisions on interventions for primary prevention of cardiovascular disease can be personalised and could facilitate targeting of treatment to those at greater than average cardiovascular disease risk. The large SMART study of 7,344 participants followed over a median of 5.9 years associated increasing systolic IAD with increased risks of vascular events in people without, but not with, pre-existing vascular disease after carefully adjusted analyses, suggesting that consideration of IAD may be most important for people at low to medium cardiovascular risk. The NHS Health Check programme is delivered to at least 1 million people annually in England generating 38,000 new diagnoses of hypertension. The findings presented here suggest that 4% of these people – over 1500 per annum, could be reclassified according to their IAD measurement from below to above the 10% QRISK2 threshold for initiation of BP and lipid lowering treatment. The low conversion rate of elevated clinic BP readings to diagnoses of hypertension based on ambulatory BP recordings emphasises the importance of the NICE diagnostic pathway in avoiding overdiagnosis and overtreatment of hypertension.

In this study BP was measured simultaneously in both arms using a specific double cuff device. The Watch BP Office device has been shown to have high specificity for AF, resulting in fewer follow-up ECGs being required where AF is not present. However, sensitivity is variable; too few irregular pulses were flagged in the current study to interpret the device’s performance in place of pulse palpation for a population eligible for NHS Health Checks. In primary care, practitioners rarely have access to equipment that can measure both arms simultaneously; they need a practical and simple method of assessment. Sequential measurement of IAD is the most practical way to implement IAD measurement in primary care. It will usually over-estimate the magnitude of IAD in comparison to simultaneous measurements, but has a high negative predictive value for a
simultaneous IAD. The INTERPRESS-IPD Collaboration and other sequentially measured cohorts have shown the associations of IAD detected by this method with all-cause mortality, cardiovascular mortality and cardiovascular events. The current pilot findings represents a proof of concept but is likely to have under-estimated the true effect of sequentially measured IADs on reclassification of risk. Ambulatory monitoring following an initial raised clinic BP reading to diagnose hypertension is cost saving due to better targeting of treatment. Taking account of IAD should direct more people to this diagnostic pathway, however the economic impact of this is, as yet, unknown. This pilot study will inform further work to validate this approach, using practical sequential methods of measurement in a larger and ethnically diverse populations more representative of the range of people seen in UK primary care.
Acknowledgements

Authors’ contributions

SHR was Chief Investigator of the Check-Up study; SHR and CEC designed this study within the Check-Up programme. CEC proposed and undertook the analyses, and drafted the manuscript. AJF and MRG undertook the Health Checks and collated the data. BN extracted and collated the dataset. SMcD advised on interpretation of findings, revision of the manuscript and dissemination of results. SHR obtained ethical approval and advised on study design, JLC supervised the study and advised on study design. All authors contributed to the manuscript and read and reviewed the final manuscript prior to publication. CEC has access to the full dataset for the study and acts as guarantor.

Ethical approval

Ethical approval for this study was granted by the National Research Ethics Service Committee South West – Cornwall & Plymouth: REC ref: 12/SW/0314.

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The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Disclosures

CEC received the sphygmomanometer used in this study from Microlife for unrestricted evaluation. He has received an honorarium from Bayer AG (unrelated to IAD work). No company has had, or will have, any involvement in the design, conduct or reporting of this study.
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Table 2. Distribution of 10-year cardiovascular risk scores for 334 participants at NHS Health Checks before and after adjustment for systolic inter-arm blood pressure difference

Figure 1. Flow of participants through Health Check protocol during study
Figure 2. Distribution of systolic inter-arm difference for 334 participants at NHS Health Checks
Figure 3. 10-year cardiovascular risk scores before (blue) and after (red) adjustment for systolic inter-arm difference
Table 1. Characteristics of 334 participants at NHS Health Checks

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Table 2. Distribution of 10-year cardiovascular risk scores for 334 participants at NHS Health Checks before and after adjustment for systolic inter-arm blood pressure difference

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¶ intervention threshold is 10-year cardiovascular risk $\geq$ 10% for QRISK2 & ASCVD, $\geq$15% for Framingham

*row proportions and means do not always total due to rounding
Figure 1. Flow of participants through Health Check protocol during study

BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = Haemoglobin A1c; AF = atrial fibrillation
Figure 2. Distribution of systolic inter-arm difference for 334 participants at NHS Health Checks
Figure 3. 10-year cardiovascular risk scores before (blue) and after (red) adjustment for systolic inter-arm difference.