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Complete List of Authors:	Taft, Charles; Goteborgs universitet Institutionen for vardvetenskap och halsa, Health and Care Sciences; Centre for Person-Centred Care (GPCC) Hallberg, Inger; Goteborgs universitet Institutionen for vardvetenskap och halsa; Centre for Person-Centred Care (GPCC) Bengtsson, Ulrika; Goteborgs universitet Institutionen for vardvetenskap och halsa; Centre for Person-Centred Care (GPCC) Manhem, Karin; Goteborgs Universitet, Institute of Medicine, Sahlgrenska Academy Kjellgren , Karin; Goteborgs universitet Institutionen for vardvetenskap och halsa; Centre for Person-Centred Care (GPCC)
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TITLE PAGE

Title:

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Authors:

Charles Taft, Associate professor of psychology, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden Charles.taft@gu.se

Inger Hallberg, researcher, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden Inger.hallberg@liu.se

Ulrika Bengtsson, researcher, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden Ulrika.bengtsson@gu.se

Karin Manhem, Professor of medicine, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; Department of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, Karin.manhem@gu.se

Karin Kjellgren, Professor of nursing, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden Karin.kjellgren@liu.se

Corresponding author: Charles Taft, Charles.taft@gu.se, Tel +46708414845

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ABSTRACT

Objectives

To explore relationships between patients' self-monitoring of blood pressure (BP) and their concurrent self-reports of medication intake, wellbeing stress, physical activity and symptoms.

Design

A prospective study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension.

Setting

Four primary health care centers situated in urban and suburban communities in Sweden.

Participants

50 patients undergoing treatment for hypertension.

Primary and Secondary Outcome Measures

Associations between systolic (SBP) and diastolic blood pressure (DBP) and 10 self-report lifestyle-related variables.

Results

Medication intake, wellbeing, stress and physical activity were associated variously with same-day SBP and DBP. The single strongest association was found between medication intake and SBP, where failure to take medications was associated with an estimated 7.44 mmHg higher SBP. To a lesser degree, medication intake was also associated with DBP. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated with only SBP. None of the symptoms dizziness, headache, restlessness, fatigue or palpitations were significantly associated with BP.

Conclusions

Our findings that BP was associated with patients' BP management behaviors and experiences of wellbeing and stress but not symptoms suggest that enabling persons with hypertension to monitor and track their BP in relation to medication intake, physical activity, wellbeing, stress and symptoms may be a fruitful way to help them gain first-hand understanding of the importance of adherence and persistence to treatment recommendations.

Trial registration

ClinicalTrials.gov registration number: NCT01510301.

Keywords

Hypertension, self-management, adherence, self-reports, stress, symptoms, wellbeing, physical activity, associations, blood pressure variability

ARTICLE SUMMARY

Strengths and limitations of this study

- The study is unique in investigating associations between self-monitored blood pressure and same-day, self-reported medication intake, wellbeing, stress, physical activity and symptoms during 56 consecutive days
- The mobile phone-based self-management support system was designed in collaboration with patients with hypertension as a tool to enable and empower patients to monitor and track their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module.
- The generalizability of the study results may be impeded by the use of convenience sampling for patient selection.

- The patients reported unusually good medication adherence during the study, suggesting the need to perform larger studies with patients with more diverse adherence levels in order to confirm our findings.

INTRODUCTION

Hypertension is the leading modifiable risk factor for premature death and global disease burden (1, 2). Reducing hypertension has been shown to lower the risk of acute myocardial infarction, stroke, kidney failure, congestive heart failure and cardiovascular death (3-5). Despite strong evidence and consensus about the treatment and control of hypertension, (6-9) nonetheless only an estimated 13.8% of adults with hypertension worldwide have their blood pressure (BP) controlled (10).

As in other chronic conditions, successful treatment outcomes in hypertension depend ultimately on effective patient self-management (11, 12, 13). However, patient adherence to hypertension treatment recommendations is notoriously poor, both with respect to medication taking (14-16) and in particular to lifestyle changes (17-19), underlining the need for supporting patients in their self-management efforts. To date, interventions aimed at supporting self-management have focused mainly on self-monitoring of BP (SMBP), educational programs, and counselling (20). SMBP has been found to contribute to improved BP control (21-23) and medication adherence (24); however, evidence for the independent effects of education and counselling remains weak (20).

It has been suggested that educational interventions have failed because they have not sufficiently understood, acknowledged and addressed patients' lay perspectives on the causation and risks of hypertension (25-27). Lay beliefs are not always consistent with

biomedical opinion (26), particularly regarding the impact of stress on BP, the experience of BP symptoms, and drug side effects, tolerance and addiction, which may partly explain why patient adherence and persistence rates are poor. For example, many patients believe that stress is the main cause of hypertension and that headache, palpitations and dizziness are caused by high BP, and hence patients may cease to adhere to treatment during periods of low stress or in the absence of symptoms (25). On the other hand, SMBP may improve medication adherence by providing direct feedback on BP levels, independent of experienced symptoms, and thereby contribute to BP control by reinforcing behaviors that lower BP (28).

Recently we reported significant BP improvements with the use of a mobile phone-based self-management support system (29). Designed in accordance with patients' expressed wishes and perceived needs for support in self-managing hypertension (30-32), the system was hence developed as a tool to enable and empower patients to explore and track variations in their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module. In follow-up interviews, patients indicated that the system helped them to gain insight into the importance of adhering to treatment advice and thereby gain control in managing their condition (33). However, the usefulness of the feedback module rests on the existence of perceptible links between BP and patient self-reports. A person-centered perspective that emphasizes the value of the patient's own experiences of BP by increased participation in care, self-reporting and documentation has earlier been shown to be beneficial (33). The purpose of the present study was to explore relationships between patients' SMBP and their concurrent self-reports of stress, physical activity, wellbeing, symptoms, and medication intake.

METHODS

This study was a secondary analysis of a prospective cohort study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension. The study took place between February and June 2012 and was approved by the Regional Ethics Board in Gothenburg, Sweden (study code 551-09 and T-100-12), conducted in accordance with the Declaration of Helsinki and registered in the Clinical Trial Protocol Registration System (ClinicalTrials.gov NCT01510301) under the acronym MIHM (Mobile phone In Hypertension Management).

Recruitment and participants

Participants were recruited using convenience sampling. Based on data from earlier studies (30), a sample size was estimated based on a standard deviation (SD) of 12 for systolic BP (SBP) and 7 for diastolic BP (DBP). For detecting a difference of 8 mmHg SBP and 5 mmHg DBP with 90% power and at a 5% significance level, the sample size was estimated to 50 patients. Seventy-three consecutive patients undergoing treatment for hypertension at four primary health care centers in southern Sweden were asked to participate. Inclusion criteria were: currently being medically treated for hypertension, age ≥ 30 years, ability to understand and read Swedish, access to a mobile phone with an internet connection. Eligible patients were informed about the study orally and in writing, and were ensured confidentiality before giving their written informed consent. In total, 54 patients agreed to participate, of whom 3 withdrew before study start.

Patient involvement

Patients with hypertension were involved in all phases of the design, development and evaluation of the mobile-phone based self-management support system. As previously

reported (30-33), the system was designed based on interviews in which patients were asked to describe what they needed to better self-manage their hypertension; iteratively developed in collaboration with patients, researchers and clinicians (30-32); evaluated for content validity, reliability and usability in focus group interviews, cognitive interviews and piloting (32); examined regarding usability and usefulness in individual patient interviews (33)

The intervention

The interactive self-management support system

As previously described in detail, the system includes four components that have not previously been integrated into the same intervention for supporting self-management of hypertension (30): 1) a module for self-reporting wellbeing, symptoms, lifestyle, medication intake and side effects of medication; 2) daily home BP and pulse measurements with a validated BP monitor; 3) tailored weekly motivational messages to encourage lifestyle changes and; 4) web-based dashboard to enable patients, as well as physicians and nurses, to examine the patient´s BP in relation to the self-reports. The communication platform for the system was developed by Circadian Questions (CQ), 21st Century Mobile (http://www.cqmobil.se)

Study procedures

Participants were instructed how to use the self-management system and BP monitors by research nurses. They were requested to perform BP measurements and self-reports every evening for eight consecutive weeks and to answer self-report items first and then to measure their BP. The data reported in through the participants' mobile phones were automatically registered in a secure database.

The system was tailored to the individual patients, such that drug side-effects items (delivered maximum twice weekly) were selected based on the patient's antihypertensive medication; use and choice of motivational messages (delivered maximum twice weekly) were based on patients' preferences; and use of daily reminders was optional.

Patient self-reports

Development and evaluation of the items comprising the self-report module are described in detail elsewhere (31, 32). Briefly, items were iteratively developed from analyses of patient and professionals (physicians, nurses, pharmacists) focus group interviews about what they considered helpful for supporting self-management of their BP. Six major areas represented by 16 items were identified: three biomedical markers (SBP, DBP and pulse); three symptoms (dizziness, headache and palpitations); four medication side-effects (swollen ankles, dryness of mouth, dry cough and micturition); five quality of life variables (general well-being, stress, restlessness, sleep and fatigue); adherence to medication (medication intake); and one lifestyle variable physical activity. Items were formulated as questions, with "today" as the timeframe. Patients rated items against five-step response scales with anchors not at all (0) - extremely (4) or very bad (0) - very well/good (4), except medication intake ("Have you taken your medication today?") which was rated on a three-step scale with options yes (0), some of it (1) and no (2). Blood pressure and pulse were measured and registered as values obtained from BP monitors.

Blood pressure self-monitoring

Patients were instructed how to measure their BP in accordance with the European Society of Hypertension Practice guidelines for home blood pressure monitoring (HBPM) (34). A home blood-pressure monitor (BP A200 AFIB; Microlife USA Inc., Clearwater, FL, USA) was used

and validated according to the international protocol of the European Society of Hypertension (35).

Data analysis

Descriptive statistics were used to characterize patient demographic and clinical variables. Repeated measures linear mixed-effects modeling was used, with SBP and DBP as dependent variables. The variance/covariance structure was specified as autoregressive to guard against violations to sphericity assumptions. All models included a random intercept. Models for the two dependent variables included all 10 self-report variables, excluding medication side-effect variables, as fixed effects. Side-effect variables were excluded because they were assessed only biweekly. Individuals with partial missing data but with at least one observation for each of the independent variables were included. Statistical significance was set to p-value < 0.05 throughout. Analyses were performed with SPSS version 22 for Windows, Chicago, IL, USA and Mathematica version 11.0 for Mac (Wolfram Research, Champaign, IL, USA).

RESULTS

Patient characteristics, co-morbidity and medication are shown in Table 1. Of the 51 recruited patients who started the study, one participated only sporadically during the first weeks and dropped out entirely after four weeks and was therefore excluded from the analyses. More men than women took part, as is common in the middle-aged, and other demographics were also comparable with the general hypertensive population in Sweden (36).

Table 1. Patient characteristics (n=50)

Females n (%)	24	(48%)
Mean age (range)	59.5	(33-81)
Mean SBP (range), mmHg[a]	142	(115-195)
Mean DBP (range), mmHg[a]	84	(61-113)
Mean years with hypertension (range)	8.5	(< 1 – 32)
Co-morbidity (%)[b]	22	(52)
Co-morbidities n (%):		
Cardiovascular disease	3	(14)
Decreased renal function	2	(9)
Diabetes	7	(32)
Musculoskeletal disorder	3	(14)
Other	7	(32)
Marital status n (%)		
Married	39	(78)
Unmarried	10	(20)
Widow / widower	1	(2)
Education n (%)		
Compulsory school (≤ 9 years)	5	(10)
High school (9-12 years)	22	(44)
University	22	(44)
Missing	1	(2)
Employment status n (%)		
Employed	28	(56)
Long-term sick leave	1	(2)
Retired	19	(38)
Missing	2	(4)

[a] Mean of patients' 3-4 baseline BP measurements

[b] Information provided by patients

Links between systolic blood pressure and self-report variables

Mixed models analysis, including all 10 independent variables, yielded significant associations between SBP and medication intake, physical activity, wellbeing and stress (Table 2). Self-reported medication intake was associated with the largest decrease in SBP, where better adherence was associated with a 3.72 mmHg decrease in SBP per reported adherence level. SBP increased 1.09 mmHg with increasing levels of stress, 1.51 mmHg with decreasing levels of wellbeing and 0.70 mmHg with decreasing levels of physical activity. Figures 1a-d show the distribution of SBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 2. Linear mixed-effect model for associations between systolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	134.40	1.93	63.14	69.57	.000	130.54-138.26
Medication intake	3.72	1.19	2311.12	3.13	.002	1.39-6.04
Phyical activity	-.70	.22	2274.21	-3.14	.002	-1.13--.26
Wellbeing	1.51	.47	2407.81	3.23	.001	.59-2.42
Stress	1.09	.36	2400.96	3.04	.002	.39-1.80
Headache	.52	.46	2389.47	1.14	.253	-.37-1.41
Sleep	.57	.29	2208.24	1.95	.052	-.00-1.15
Dizziness	-.69	.65	2381.66	-1.05	.293	-1.97-.59
Palpitation	-.14	.57	2406.14	-.24	.808	-1.25-.98
Fatigue	-.32	.33	2364.10	-.98	.328	-.96-.32
Restless	.88	.55	2403.86	1.59	.113	-.21-1.96

Figures 1a-d about here

Links between diastolic blood pressure and self-report variables

A model including all 10 self-report variables showed significant associations between medication intake, wellbeing and stress (Table 3). Self-reported medication intake was associated with the largest decrease in DBP, where better adherence was associated with a 2.35 mmHg decrease in DBP per reported adherence level. Higher levels of stress and poorer wellbeing were associated with small DBP increases (0.81, 0.70 mmHg/ scale step, respectively). Figures 2a-d show the distribution of DBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 3. Linear mixed-effect model for associations between diastolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	78.44	1.00	69.14	78.43	.000	76.44-80.43
Medication intake	2.35	.71	2326.88	3.31	.001	.96-3.77
Physical activity	-.11	.13	2300.01	-.79	.428	-.37-.15
Wellbeing	.70	.28	2411.21	2.51	.012	.15-1.24
Stress	.81	.22	2404.96	3.79	.000	.39-1.23
Headache	.52	.27	2383.25	1.92	.055	-.01-1.05
Sleep	.30	.18	2239.18	1.69	.090	-.05-.64
Dizziness	-.60	.39	2390.90	-1.52	.128	-1.36-.17
Palpitations	.11	.34	2415.45	.32	.746	-.55-.77
Fatigue	-.178	.20	2383.60	-.88	.381	-.55-.21
Restless	.28	.33	2408.78	.85	.395	-.37-.93

Figures 2a-d about here

DISCUSSION

Our results showed that patient self-reports of medication intake, wellbeing, stress and physical activity were associated variously with same-day SBP and DBP. The single strongest association was found between medication intake and SBP, where failure to take medications was associated with an estimated 7.44 mmHg higher SBP. To a lesser degree, medication intake was also associated with DBP, where DBP was 4.70 mmHg higher in cases where medications were not taken. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated only with SBP. None of the assessed symptoms (dizziness, headache, wellbeing, fatigue and palpitations) were significantly associated with BP, although a near significant association was seen between headache and DBP.

To our knowledge this is the first study to report independent effects of self-reported non-adherence to medication on same-day BP. Our results, particularly regarding SBP, corroborate and extend longer-term BP effects reported by, for example, Rose et al. (37) that week-long periods of poor adherence are associated with about 12-15/7-8 mmHg higher BP than good adherence, by Hedna et al. (38) that non-adherence during a one-month period is associated with higher odds of elevated BP, as well as earlier studies showing longer term

effects of non-adherence on BP control (39, 40). These findings may potentially be exploited in SMBP-based self-management programs to help hypertensives gain an understanding of the immediate impact of hypertensive medication on BP and thereby reinforce medication adherence and persistence.

Self-reported wellbeing and stress were significantly associated with same-day BP. Again, stronger effects were seen in relation to SBP, where SBP was an estimated 4.53 mmHg higher when wellbeing was rated poor than when rated good and 3.27 mmHg higher when stress was high versus low. Corresponding DBP values were 2.10 for wellbeing and 2.43 for stress. Our findings corroborate links between BP and subjective wellbeing reported among hypertensive patients with coronary artery disease (41) and lend some support to the lay notion that hypertension is not asymptomatic (25). Moreover, our findings regarding stress are in line with a large body of research showing strong and consistent associations between stress and increases in BP levels (42, 43). Although BP spikes associated with acute stress are normal physiological reactions to stressors, chronic stress is acknowledged as an important risk factor for cardiovascular disorders and events. (43). It may therefore be beneficial to monitor stress levels in connection with SMBP, both to help patients understand the importance of stress avoidance and to help clinicians assess the need for instituting stress reduction therapy.

High levels of self-reported physical activity were associated with moderately lower levels of same-day SBP (-2.10 mmHg). This finding was not unexpected given that BP-mitigating effects of physical activity are yielded after sustained periods of training (44). Physical activity is a recommended lifestyle modification for the prevention and management of hypertension (45) and tracking physical activity in relation to BP may help to motivate patients to adhere to this recommendation.

No significant associations were found between symptoms (dizziness, headache and palpitations) and BP, although a near significant association (p=.055) was found between headache and DBP. The lack of associations between symptoms and BP may possibly be due to the fact that patients reported few symptoms during the study period. Nevertheless, our finding is in line with earlier studies indicating a lack of association between elevated BP and symptoms (dizziness, headache and palpitations) (46, 47). Monitoring symptoms in connection with SMBP may, however, serve to inform patients who base their medication intake on the presence or absence of symptoms (25) that symptom experience is an imperfect indicator of BP levels.

There are a number of limitations to this study. Although the socio-demographic distribution of the sample corresponded to that of the hypertensive population in Sweden (36), the sample was selected using convenience sampling, which has clear-cut implications for the generalizability of our results. The patient sample also reported unusually good medication adherence during the study, where only 11 cases of nonadherence were reported over the course of the 8-week study period. Larger and randomized studies including patients with more diverse adherence levels are needed to confirm our findings.

CONCLUSIONS

The mobile-phone based self-management system was developed to empower patients and enable practitioners to monitor and track BP in relation to medication intake, physical activity, wellbeing, stress and symptoms. The robust and prompt effect of appropriate drug intake may help patients to gain first-hand understanding of the importance of adherence and persistence to treatment recommendations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

BP control in treated hypertensives is suboptimal due largely to poor adherence to treatment.

SMBP contributes to improved BP control and medication adherence, whereas evidence supporting education and counselling interventions is weak.

WHAT THIS STUDY ADDS

Significant same-day associations were evidenced between BP and medication intake, stress, physical activity and wellbeing; however, symptoms patients often associate with high BP were not associated with BP.

The mobile phone system enables patients to monitor and track BP in relation to patient behaviors and experiences and may have important implications for adherence to treatment recommendations by helping patients gain first-hand insight into the blood pressure lowering effects of medication intake and physical activity, stress avoidance, etc. and inform patients who base adherence decisions on symptom experience that symptoms are poor indicators of blood pressure levels.

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COMPETING INTERESTS

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

TRANSPARENCY DECLARATION

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that discrepancies from the study as planned have been explained.

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DATA SHARING

Patient level data may be obtained by contacting the corresponding author. Consent for data sharing was not obtained from participants but the presented data are anonymized and risk of identification is low.

CONTRIBUTORS

CT designed the study, performed data analyses, and drafted and revised the paper. He is guarantor. IH designed the study, monitored data collection and revised the paper. UB designed the study, monitored data collection and revised the paper. KM drafted and revised the paper. KK initiated the project, designed the study, and drafted and revised the paper. She is guarantor.

All authors have approved the submitted manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA SHARING STATEMENT

There are no additional data available for data sharing.

Figure legends

Figures 1a-d. Distributions of SBP values by reported level of medication intake (three-step response scale), stress, wellbeing and physical activity (five-step response scale). Regression lines for the relationships between SBP and the independent variables are shown in red. Colors denote concentrations of SBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept SBP value (135 mmHg).

Figures 2a-c Distributions of DBP values by reported level of medication intake (three-step response scale), stress and wellbeing (five-step response scale). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg).

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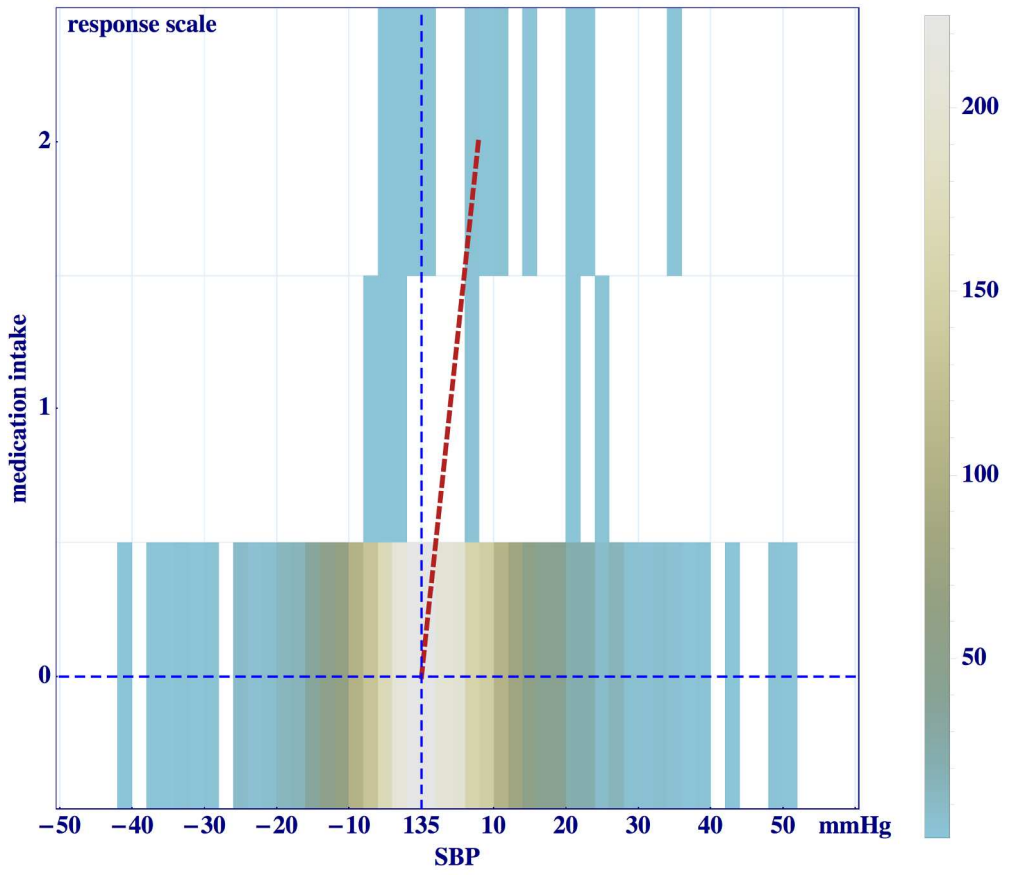

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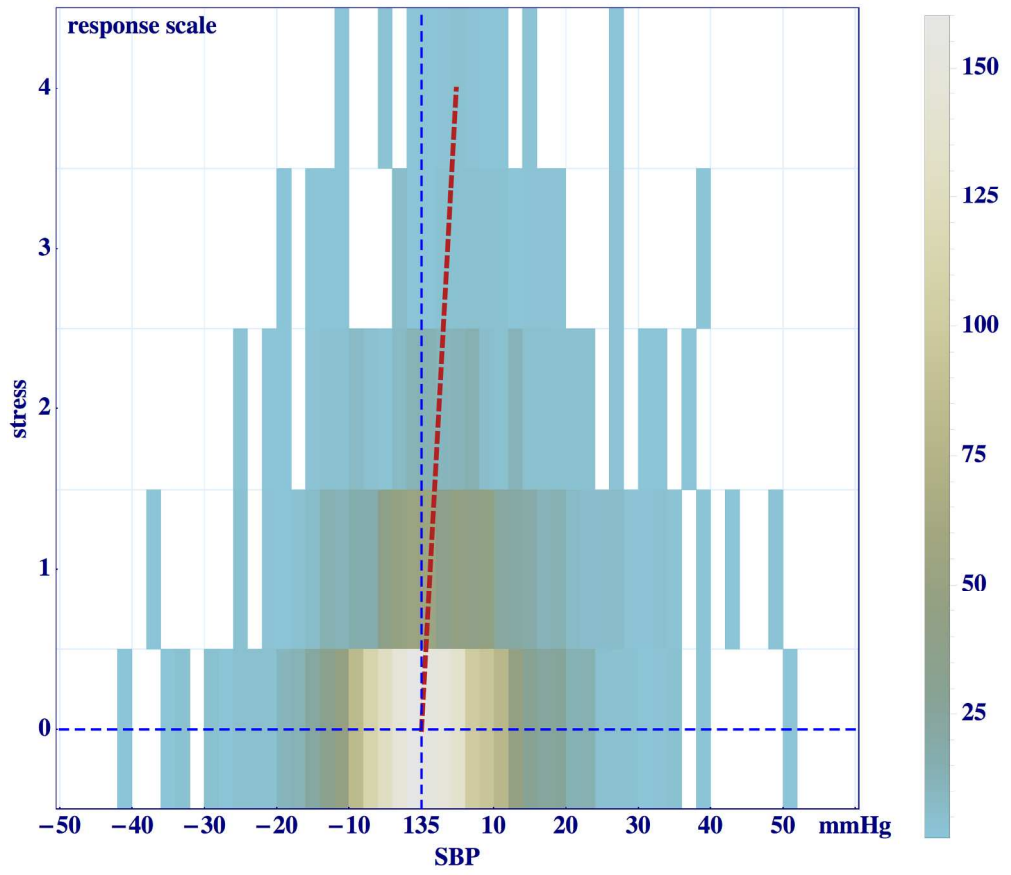

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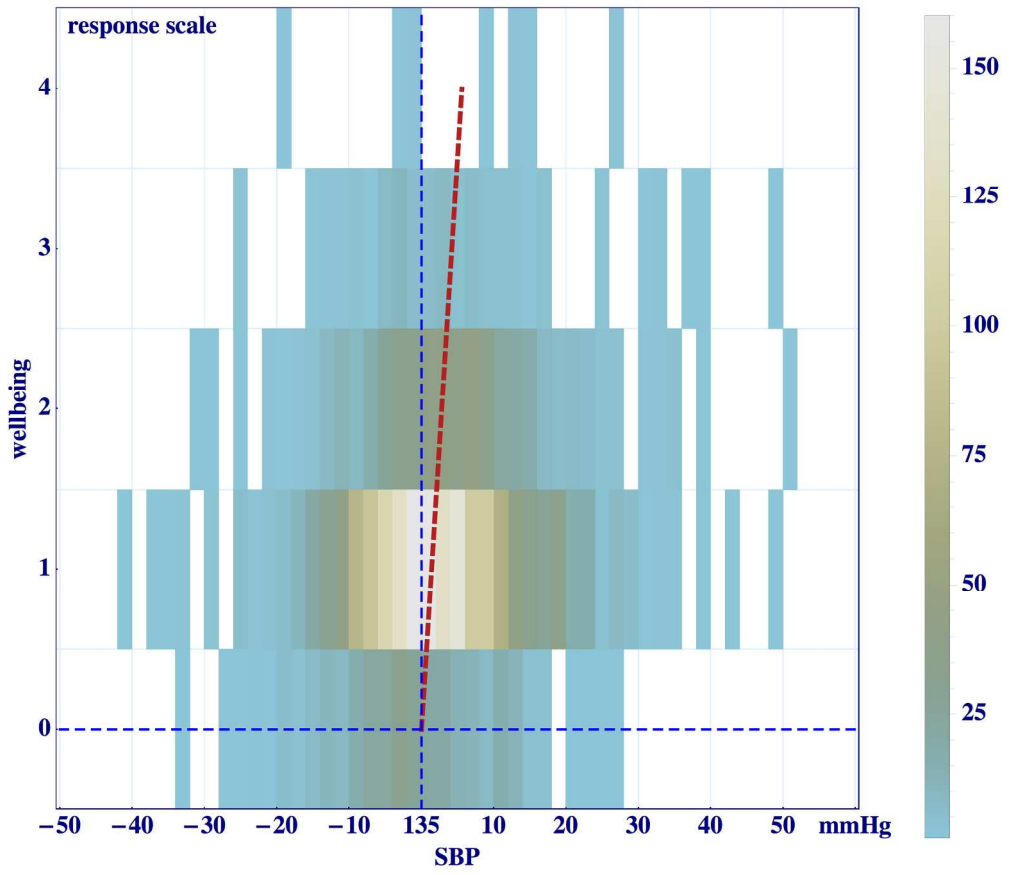

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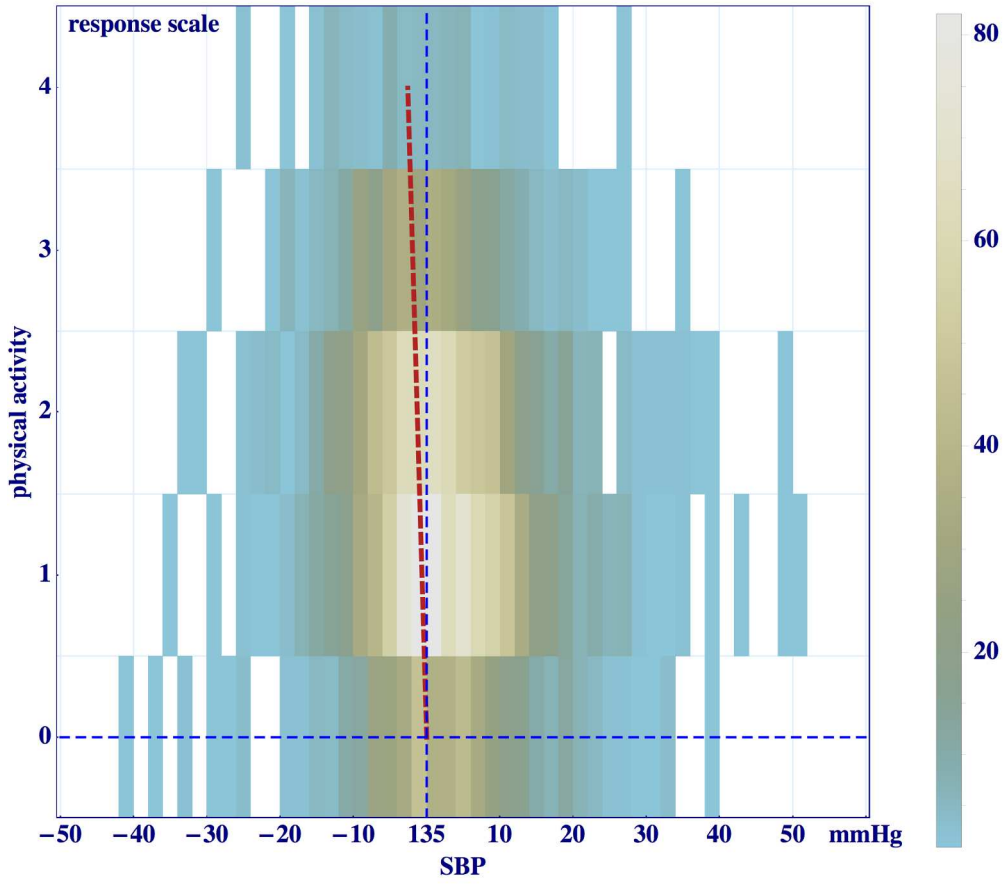

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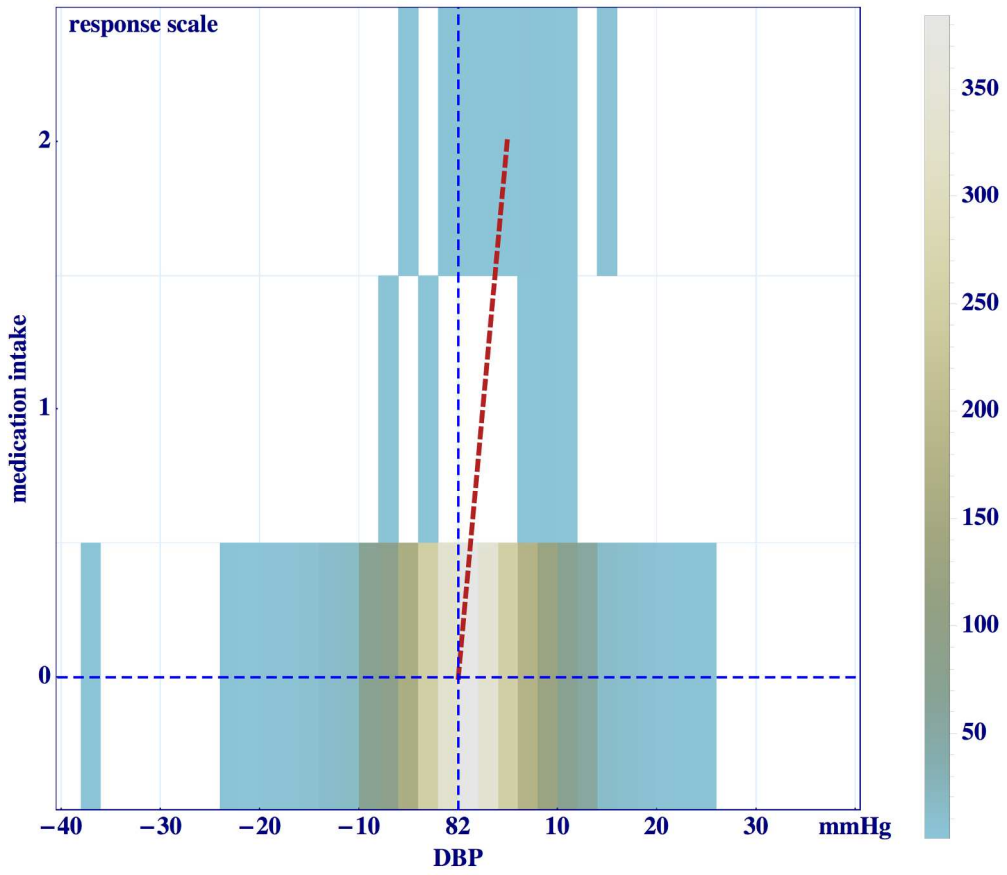

Figures 2a-c Distributions of DBP values by reported level of medication intake (three-step response scale), stress and wellbeing (five-step response scale). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg).

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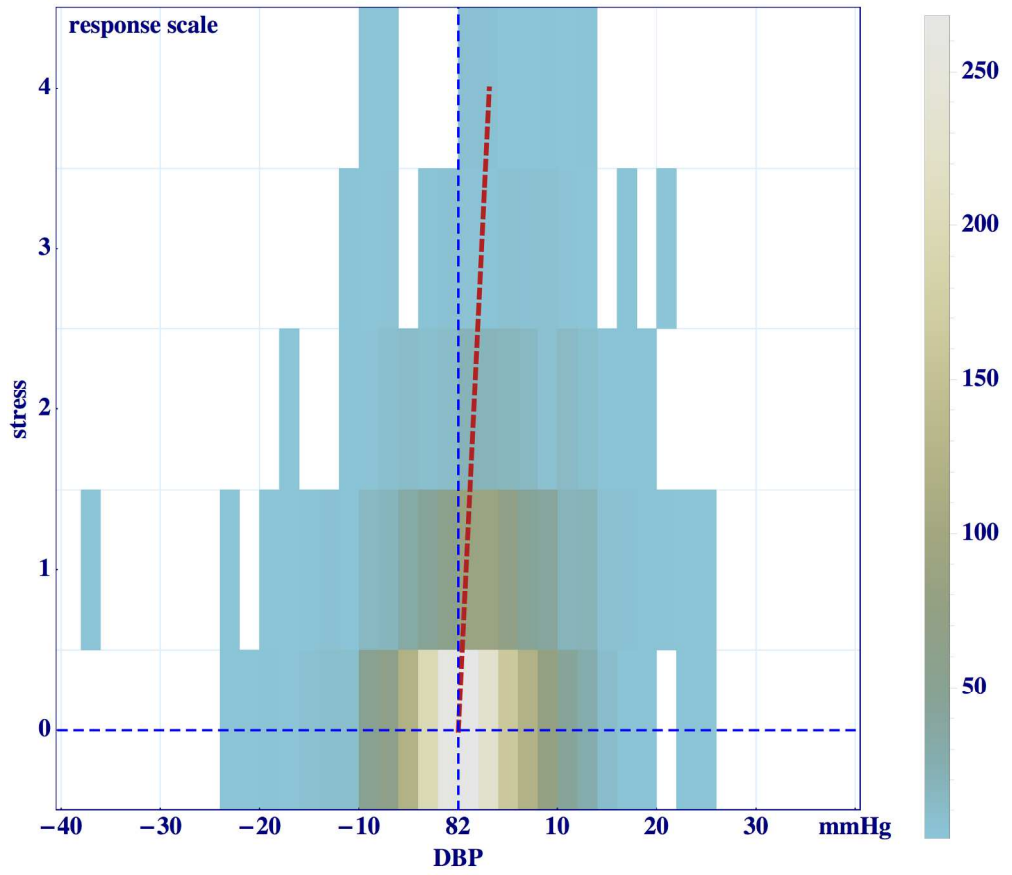

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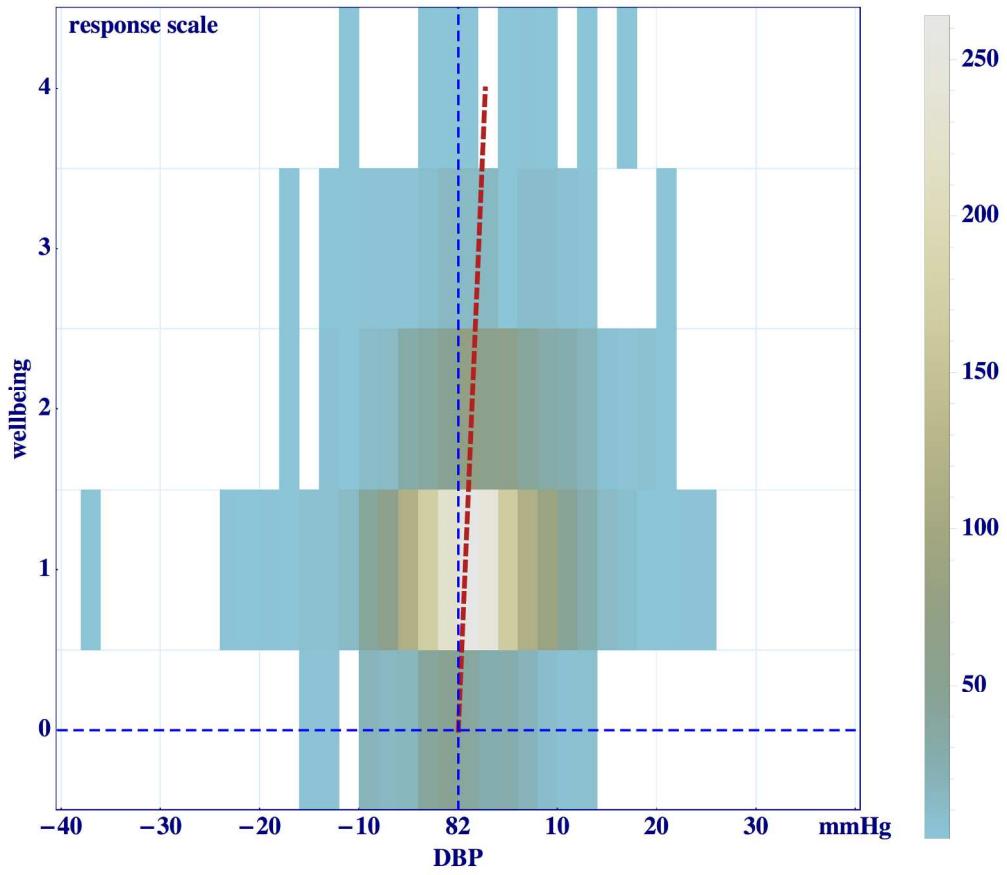

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Links between blood pressure and medication intake, wellbeing, stress, physical activity and symptoms reported via a mobile phone-based self-management support system - a cohort study in primary care

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TITLE PAGE

Title:

Links between blood pressure and medication intake, wellbeing, stress, physical activity and symptoms reported via a mobile phone-based self-management support system – a cohort study in primary care

Authors:

Charles Taft, Associate professor of psychology, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Charles.taft@gu.se

Inger Hallberg, researcher, Department of Medical and Health Sciences, Linköping University, SE-581 83 Linköping, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Inger.hallberg@liu.se

Ulrika Bengtsson, researcher, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Ulrika.bengtsson@gu.se

Karin Manhem, Professor of medicine, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; Department

of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, Karin.manhem@gu.se

Karin Kjellgren, Professor of nursing, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Karin.kjellgren@liu.se

Corresponding author: Charles Taft, Charles.taft@gu.se, Tel +46708414845

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ABSTRACT

Objectives

To explore relationships between patients' self-monitoring of blood pressure (BP) and their concurrent self-reports of medication intake, wellbeing stress, physical activity and symptoms.

Design

The study is a secondary analysis of a prospective study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension.

Setting

Four primary health care centers situated in urban and suburban communities in Sweden.

Participants

50 patients undergoing treatment for hypertension.

Primary and Secondary Outcome Measures

Associations between systolic (SBP) and diastolic blood pressure (DBP) and 10 self-report lifestyle-related variables were analyzed using linear mixed-effects modelling.

Results

Medication intake, wellbeing, stress and physical activity were associated variously with same-day SBP and DBP. The single strongest association was found between medication intake and SBP, where failure to take medications was associated with an estimated 7.44 mmHg higher SBP. To a lesser degree, medication intake was also associated with DBP, where DBP was 4.70 mmHg higher in cases where medications were not taken. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated with only SBP. None of the symptoms dizziness, headache, restlessness, fatigue or palpitations were significantly associated with BP.

Conclusions

Our findings that BP was associated with patients' BP management behaviors and experiences of wellbeing and stress but not symptoms suggest that enabling persons with hypertension to monitor and track their BP in relation to medication intake, physical activity, wellbeing, stress and symptoms may be a fruitful way to help them gain first-hand understanding of the importance of adherence and persistence to treatment recommendations.

Trial registration

ClinicalTrials.gov registration number: NCT01510301.

Keywords

Hypertension, self-management, adherence, self-reports, stress, symptoms, wellbeing, physical activity, associations, blood pressure variability

ARTICLE SUMMARY

Strengths and limitations of this study

- The study is unique in investigating associations between self-monitored blood pressure and same-day, self-reported medication intake, wellbeing, stress, physical activity and symptoms during 56 consecutive days
- The mobile phone-based self-management support system was designed in collaboration with patients with hypertension as a tool to enable and empower patients to monitor and track their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module.
- The generalizability of the study results may be impeded by the use of convenience sampling for patient selection.

- The patients reported unusually good medication adherence during the study, suggesting the need to perform larger studies with patients with more diverse adherence levels in order to confirm our findings.

INTRODUCTION

Hypertension is the leading modifiable risk factor for premature death and global disease burden (1, 2). Reducing hypertension has been shown to lower the risk of acute myocardial infarction, stroke, kidney failure, congestive heart failure and cardiovascular death (3-5). Despite strong evidence and consensus about the treatment and control of hypertension, (6-9) nonetheless only an estimated 13.8% of adults with hypertension worldwide have their blood pressure (BP) controlled (10).

As in other chronic conditions, successful treatment outcomes in hypertension depend ultimately on effective patient self-management (11, 12, 13). However, patient adherence to hypertension treatment recommendations is notoriously poor, both with respect to medication taking (14-16) and in particular to lifestyle changes (17-19), underlining the need for supporting patients in their self-management efforts. To date, interventions aimed at supporting self-management have focused mainly on self-monitoring of BP (SMBP), educational programs, and counselling (20). SMBP has been found to contribute to improved BP control (21-23) and medication adherence (24); however, evidence for the independent effects of education and counselling remains weak (20).

It has been suggested that educational interventions have failed because they have not sufficiently understood, acknowledged and addressed patients' lay perspectives on the causation and risks of hypertension (25-27). Lay beliefs are not always consistent with

biomedical opinion (26), particularly regarding the impact of stress on BP, the experience of BP symptoms, and drug side effects, tolerance and addiction, which may partly explain why patient adherence and persistence rates are poor. For example, many patients believe that stress is the main cause of hypertension and that headache, palpitations and dizziness are caused by high BP, and hence patients may cease to adhere to treatment during periods of low stress or in the absence of symptoms (25). On the other hand, SMBP may improve medication adherence by providing direct feedback on BP levels, independent of experienced symptoms, and thereby contribute to BP control by reinforcing behaviors that lower BP (28).

This study is part of a research program aimed at developing and evaluating a mobile phone-based self-management system to support hypertension self-management. Recently we reported significant BP improvements with the use of the system (29). Designed in accordance with patients' expressed wishes and perceived needs for support in self-managing hypertension (30-32), the system was hence developed as a tool to enable and empower patients to explore and track variations in their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module. In follow-up interviews, patients indicated that the system helped them to gain insight into the importance of adhering to treatment advice and thereby gain control in managing their condition (33). However, the usefulness of the feedback module rests on the existence of perceptible links between BP and patient self-reports. A person-centered perspective that emphasizes the value of the patient's own experiences of BP by increased participation in care, self-reporting and documentation has earlier been shown to be beneficial (33). The purpose of the present study was to explore relationships between patients' SMBP and their concurrent self-reports of stress, physical activity, wellbeing, symptoms, and medication intake.

METHODS

This study was a secondary analysis of a prospective cohort study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension. The study took place between February and June 2012 and was approved by the Regional Ethics Board in Gothenburg, Sweden (study code 551-09 and T-100-12), conducted in accordance with the Declaration of Helsinki and registered in the Clinical Trial Protocol Registration System (ClinicalTrials.gov NCT01510301) under the acronym MIHM (Mobile phone In Hypertension Management).

Recruitment and participants

Participants were recruited using convenience sampling. Based on data from earlier studies (29), a sample size was estimated based on a standard deviation (SD) of 12 for systolic BP (SBP) and 7 for diastolic BP (DBP). For detecting a difference of 8 mmHg SBP and 5 mmHg DBP with 90% power and at a 5% significance level, the sample size was estimated to 50 patients. Seventy-three consecutive patients undergoing treatment for hypertension at four primary health care centers in southern Sweden were asked to participate. Inclusion criteria were: currently being medically treated for hypertension, age ≥ 30 years, ability to understand and read Swedish, access to a mobile phone with an internet connection. Eligible patients were informed about the study orally and in writing, and were ensured confidentiality before giving their written informed consent. In total, 54 patients agreed to participate, of whom 3 withdrew before study start.

Patient involvement

Patients with hypertension were involved in all phases of the design, development and evaluation of the mobile-phone based self-management support system. The research question for this study was generated from patient interviews (33) and its merits were confirmed in interviews with professionals. Patients were not involved in drafting the paper. As previously reported (30-33), the system was designed based on interviews in which patients were asked to describe what they needed to better self-manage their hypertension; iteratively developed in collaboration with patients, researchers and clinicians (30-32); evaluated for content validity, reliability and usability in focus group interviews, cognitive interviews and piloting (32); examined regarding usability and usefulness in individual patient interviews (33)

The intervention

The interactive self-management support system

As previously described in detail, the system includes four components that have not previously been integrated into the same intervention for supporting self-management of hypertension (29): 1) a module for self-reporting wellbeing, symptoms, lifestyle, medication intake and side effects of medication; 2) daily home BP and pulse measurements with a validated BP monitor; 3) tailored weekly motivational messages to encourage lifestyle changes and; 4) web-based dashboard to enable patients, as well as physicians and nurses, to examine the patient´s BP in relation to the self-reports. The communication platform for the system was developed by Circadian Questions (CQ), 21st Century Mobile (http://www.cqmobil.se)

Study procedures

Participants were instructed how to use the self-management system and BP monitors by research nurses. They were requested to perform BP measurements and self-reports every evening for eight consecutive weeks and to answer self-report items first and then to measure their BP. The actual order in which these two tasks were performed could not be determined from the database, although in the report interface the items were provided first, after which space for BP registration was given. In subsequent interviews participants confirmed that they followed the instructed order (33). The data reported in through the participants' mobile phones were automatically registered in a secure database.

The system was tailored to the individual patients, such that drug side-effects items (delivered maximum twice weekly) were selected based on the patient's antihypertensive medication; use and choice of motivational messages (delivered maximum twice weekly) were based on patients' preferences; and use of daily reminders was optional.

Patient self-reports

Development and evaluation of the items comprising the self-report module are described in detail elsewhere (31, 32). Briefly, items were iteratively developed from analyses of patient and professionals (physicians, nurses, pharmacists) focus group interviews about what they considered helpful for supporting self-management of their BP. Six major areas represented by 16 items were identified: three biomedical markers (SBP, DBP and pulse); three symptoms (dizziness, headache and palpitations); four medication side-effects (swollen ankles, dryness of mouth, dry cough and micturition); five quality of life variables (general well-being, stress, restlessness, sleep and fatigue); adherence to medication (medication intake); and one lifestyle variable physical activity. Items were formulated as questions, with "today" as the timeframe. Patients rated items against five-step response scales with anchors not at all (0) - extremely (4) or very bad (0) - very well/good (4), except medication intake ("Have you taken your

medication today?") which was rated on a three-step scale with options yes (0), some of it (1) and no (2) and wellbeing with an inverse five-step scale from very good (0) to very bad (4). Blood pressure and pulse were measured and registered as values obtained from BP monitors.

Blood pressure self-monitoring

Patients were instructed how to measure their BP in accordance with the European Society of Hypertension Practice guidelines for home blood pressure monitoring (HBPM) (34). A home blood-pressure monitor (BP A200 AFIB; Microlife USA Inc., Clearwater, FL, USA) was used and validated according to the international protocol of the European Society of Hypertension (35).

Data analysis

Descriptive statistics were used to characterize patient demographic and clinical variables. Repeated measures linear mixed-effects modeling was used, with SBP and DBP as dependent variables. The variance/covariance structure was specified as autoregressive to guard against violations to sphericity assumptions. All models included a random intercept. Models for the two dependent variables included all 10 self-report variables, excluding medication side-effect variables, as fixed effects. Side-effect variables were excluded because they were assessed only biweekly. Individuals with partial missing data but with at least one observation for each of the independent variables were included. As customary in similar blood pressure studies, day one of the study was excluded from analyses due to abnormally high blood pressure values, hence 55 days were analyzed. Statistical significance was set to p-value < 0.05 throughout. Analyses were performed with SPSS version 22 for Windows, Chicago, IL, USA and Mathematica version 11.0 for Mac (Wolfram Research, Champaign, IL, USA).

RESULTS

Patient characteristics, co-morbidity and medication are shown in Table 1. Of the 51 recruited patients who started the study, one participated only sporadically during the first weeks and dropped out entirely after four weeks and was therefore excluded from the analyses. More men than women took part, as is common in the middle-aged, and other demographics were also comparable with the general hypertensive population in Sweden (36). The self-reported BP data were validated against the BP values saved in the BP monitor. Among 14 consecutive patients selected for comparison (33), only 21 values of 1448 of both SBP and DBP differed.

Table 1. Patient characteristics (n=50)

Females n (%)	24 (48%)
Mean age (range)	59.5 (33-81)
Mean SBP (range), mmHg[a]	142 (115-195)
Mean DBP (range), mmHg[a]	84 (61-113)
Mean years with hypertension (range)	8.5 (< 1 – 32)
Co-morbidity n, (%)[b]	22 (52)
Co-morbidities n (%):	
Cardiovascular disease	3 (14)
Decreased renal function	2 (9)
Diabetes	7 (32)
Musculoskeletal disorder	3 (14)
Other	7 (32)

Type of antihypertensive medication, n.		
Diuretics	12	
Potassium-sparing diuretics	4	
β-blockers	18	
Calcium channel blockers	22	
ACE inhibitors	11	
Angiotensin II receptor antagonists	21	
ACE inhibitors+diuretic	1	
Angiotensin II receptor antagonist+diuretic	5	
Number of antihypertensive medications, n.		
One	19	
Two	19	
Three	11	
Four	1	
Marital status		
Married	39	(78)
Unmarried	10	(20)
Widow / widower	1	(2)
Education, n (%)		
Compulsory school (≤ 9 years)	5	(10)
High school (9-12 years)	22	(44)
University	22	(44)
Missing	1	(2)
Employment status, n (%)		
Employed	28	(56)
Long-term sick leave	1	(2)

Retired	19	(38)
Missing	2	(4)

[a] Mean of patients' 3-4 baseline BP measurements

[b] Information provided by patients

Links between systolic blood pressure and self-report variables

Mixed models analysis, including all 10 independent variables, yielded significant associations between SBP and medication intake, physical activity, wellbeing and stress (Table 2). Self-reported medication intake was associated with the largest decrease in SBP, where better adherence was associated with a 3.72 mmHg decrease in SBP per reported adherence level. SBP increased 1.09 mmHg with increasing levels of stress, 1.51 mmHg with decreasing levels of wellbeing and 0.70 mmHg with decreasing levels of physical activity. Figures 1a-d show the distribution of SBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 2. Linear mixed-effect model for associations between systolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	134.40	1.93	63.14	69.57	.000	130.54-138.26
Medication intake	3.72	1.19	2311.12	3.13	.002	1.39-6.04
Phyical activity	-.70	.22	2274.21	-3.14	.002	-1.13--.26
Wellbeing	-1.51	.47	2407.81	-3.23	.001	-.59--2.42
Stress	1.09	.36	2400.96	3.04	.002	.39-1.80
Headache	.52	.46	2389.47	1.14	.253	-.37-1.41
Sleep	.57	.29	2208.24	1.95	.052	-.00-1.15
Dizziness	-.69	.65	2381.66	-1.05	.293	-1.97-.59
Palpitation	-.14	.57	2406.14	-.24	.808	-1.25-.98
Fatigue	-.32	.33	2364.10	-.98	.328	-.96-.32
Restless	.88	.55	2403.86	1.59	.113	-.21-1.96

Figure panels 1a-d about here

Links between diastolic blood pressure and self-report variables

A model including all 10 self-report variables showed significant associations between medication intake, wellbeing and stress (Table 3). Self-reported medication intake was associated with the largest decrease in DBP, where better adherence was associated with a 2.35 mmHg decrease in DBP per reported adherence level. Higher levels of stress and poorer wellbeing were associated with small DBP increases (0.81, 0.70 mmHg/ scale step,

respectively). Figures 2a-c show the distribution of DBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 3. Linear mixed-effect model for associations between diastolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	78.44	1.00	69.14	78.43	.000	76.44-80.43
Medication intake	2.35	.71	2326.88	3.31	.001	.96-3.77
Physical activity	-.11	.13	2300.01	-.79	.428	-.37-.15
Wellbeing	-.70	.28	2411.21	-2.51	.012	-.15--1.24
Stress	.81	.22	2404.96	3.79	.000	.39-1.23
Headache	.52	.27	2383.25	1.92	.055	-.01-1.05
Sleep	.30	.18	2239.18	1.69	.090	-.05-.64
Dizziness	-.60	.39	2390.90	-1.52	.128	-1.36-.17
Palpitations	.11	.34	2415.45	.32	.746	-.55-.77
Fatigue	-.178	.20	2383.60	-.88	.381	-.55-.21
Restless	.28	.33	2408.78	.85	.395	-.37-.93

Figure panels 2a-c about here

DISCUSSION

Our results showed that patient self-reports of medication intake, wellbeing, stress and physical activity were associated variously with same-day SBP and DBP. The single strongest

association was found between medication intake and SBP, where failure to take medications was associated with an estimated 7.44 mmHg higher SBP. To a lesser degree, medication intake was also associated with DBP, where DBP was 4.70 mmHg higher in cases where medications were not taken. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated only with SBP. None of the assessed symptoms (dizziness, headache, wellbeing, fatigue and palpitations) were significantly associated with BP, although a near significant association was seen between headache and DBP.

To our knowledge this is the first study to report independent effects of self-reported non-adherence to medication on same-day BP. Our results, particularly regarding SBP, corroborate and extend longer-term BP effects reported by, for example, Rose et al. (37) that week-long periods of poor adherence are associated with about 12-15/7-8 mmHg higher BP than good adherence, by Hedna et al. (38) that non-adherence during a one-month period is associated with higher odds of elevated BP, as well as earlier studies showing longer term effects of non-adherence on BP control (39, 40). We also have analyzed the effects of using the mobile phone system over eight-weeks and found significant decreases in SBP (-7 mmHg) and DBP (-4.9 mmHg) (29). Our findings of same-day associations may potentially be exploited in SMBP-based self-management programs to help hypertensives gain an understanding of the immediate impact of hypertensive medication on BP and thereby reinforce medication adherence and persistence. However, caution should be observed in interpreting our results given that few instances of partial or nonadherence were reported over the course of the 8-week study period.

Self-reported wellbeing and stress were significantly associated with same-day BP. Again, stronger effects were seen in relation to SBP, where SBP was an estimated 4.53 mmHg higher when wellbeing was rated poor than when rated good and 3.27 mmHg higher when stress was high versus low. Corresponding DBP values were 2.10 for wellbeing and 2.43 for stress. Our findings corroborate links between BP and subjective wellbeing reported among hypertensive patients with coronary artery disease (41) and lend some support to the lay notion that hypertension is not asymptomatic (25). Moreover, our findings regarding stress are in line with a large body of research showing strong and consistent associations between stress and increases in BP levels (42, 43). Although BP spikes associated with acute stress are normal physiological reactions to stressors, chronic stress is acknowledged as an important risk factor for cardiovascular disorders and events. (43). It may therefore be beneficial to monitor stress levels in connection with SMBP, both to help patients understand the importance of stress avoidance and to help clinicians assess the need for instituting stress reduction therapy.

High levels of self-reported physical activity were associated with moderately lower levels of same-day SBP (-2.10 mmHg). This finding was not unexpected given that BP-mitigating effects of physical activity are yielded after sustained periods of training (44). Physical activity is a recommended lifestyle modification for the prevention and management of hypertension (45) and tracking physical activity in relation to BP may help to motivate patients to adhere to this recommendation.

No significant associations were found between symptoms (dizziness, headache and palpitations) and BP, although a near significant association (p=.055) was found between headache and DBP. The lack of associations between symptoms and BP may possibly be due to the fact that patients reported few symptoms during the study period. Nevertheless, our

finding is in line with earlier studies indicating a lack of association between elevated BP and symptoms (dizziness, headache and palpitations) (46, 47). Monitoring symptoms in connection with SMBP may, however, serve to inform patients who base their medication intake on the presence or absence of symptoms (25) that symptom experience is an imperfect indicator of BP levels.

There are a number of limitations to this study. Although the socio-demographic distribution of the sample corresponded to that of the hypertensive population in Sweden (36), the sample was selected using convenience sampling, which has clear-cut implications for the generalizability of our results. The patient sample also reported unusually good medication adherence during the study, where only 11 patients reported any nonadherence (in total 7 reports of partial medication intake and 15 of no medication intake) were reported over the course of the 8-week study period. We cannot preclude that our high adherence rates may owe to sampling, reactivity or social desirability bias. Larger and randomized studies including patients with more diverse adherence levels are needed to confirm our findings.

CONCLUSIONS

Significant same-day associations were evidenced between BP and medication intake, stress, physical activity and wellbeing; however, symptoms that patients often associate with high BP were not associated with BP.

The mobile phone system enables patients to monitor and track BP in relation to patient behaviors and experiences and may have important implications for adherence to treatment recommendations by helping patients gain first-hand insight into the blood pressure lowering effects of medication intake and physical activity, stress avoidance, etc. and inform patients

who base adherence decisions on symptom experience that symptoms are poor indicators of blood pressure levels.

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COMPETING INTERESTS

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

TRANSPARENCY DECLARATION

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that discrepancies from the study as planned have been explained.

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DATA SHARING STATEMENT

Patient level data may be obtained by contacting the corresponding author. There are no additional data available for data sharing. Consent for data sharing was not obtained from participants but the presented data are anonymized and risk of identification is low.

CONTRIBUTORS

CT designed the study, performed data analyses, and drafted and revised the paper. He is guarantor. IH designed the study, monitored data collection and revised the paper. UB designed the study, monitored data collection and revised the paper. KM drafted and revised the paper. KK initiated the project, designed the study, and drafted and revised the paper. She is guarantor.

All authors have approved the submitted manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure legends

Figures 1a-d. Distributions of SBP values by reported level of medication intake (yes-some-no), stress (no-high), wellbeing (good-poor) and physical activity (no-high). Regression lines for the relationships between SBP and the independent variables are shown in red. Colors denote concentrations of SBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept SBP value (135 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

Figures 2a-c Distributions of DBP values by reported level of medication intake (yes-some-no), stress (no-high) and wellbeing (good-poor). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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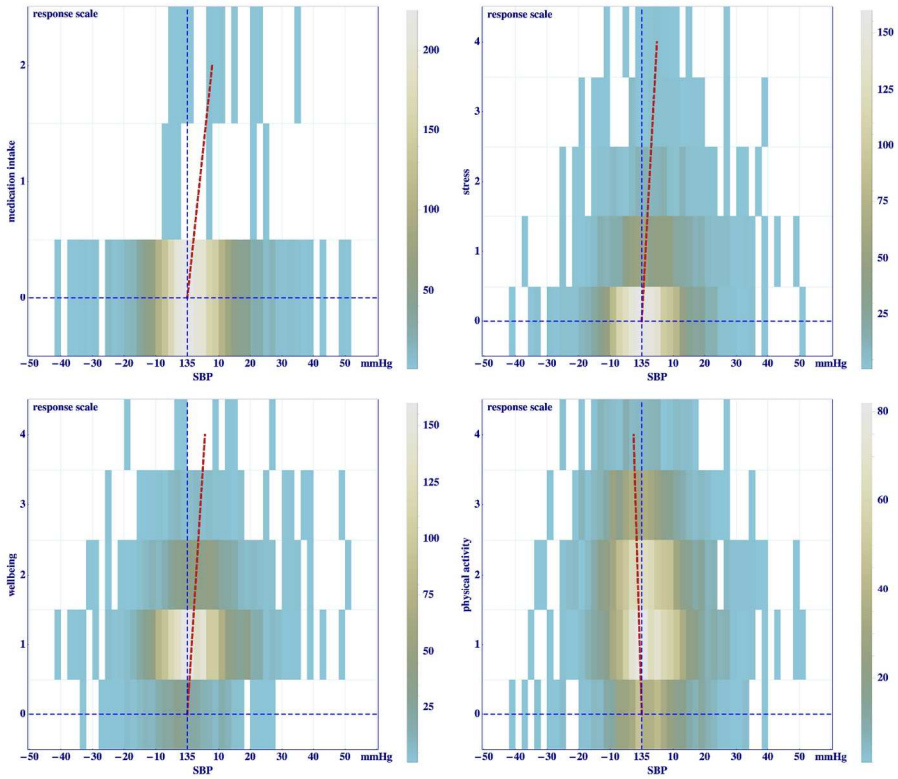

Figures 1a-d. Distributions of SBP values by reported level of medication intake (yes-some-no), stress (no-high), wellbeing (good-poor) and physical activity (no-high). Regression lines for the relationships between SBP and the independent variables are shown in red. Colors denote concentrations of SBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept SBP value (135 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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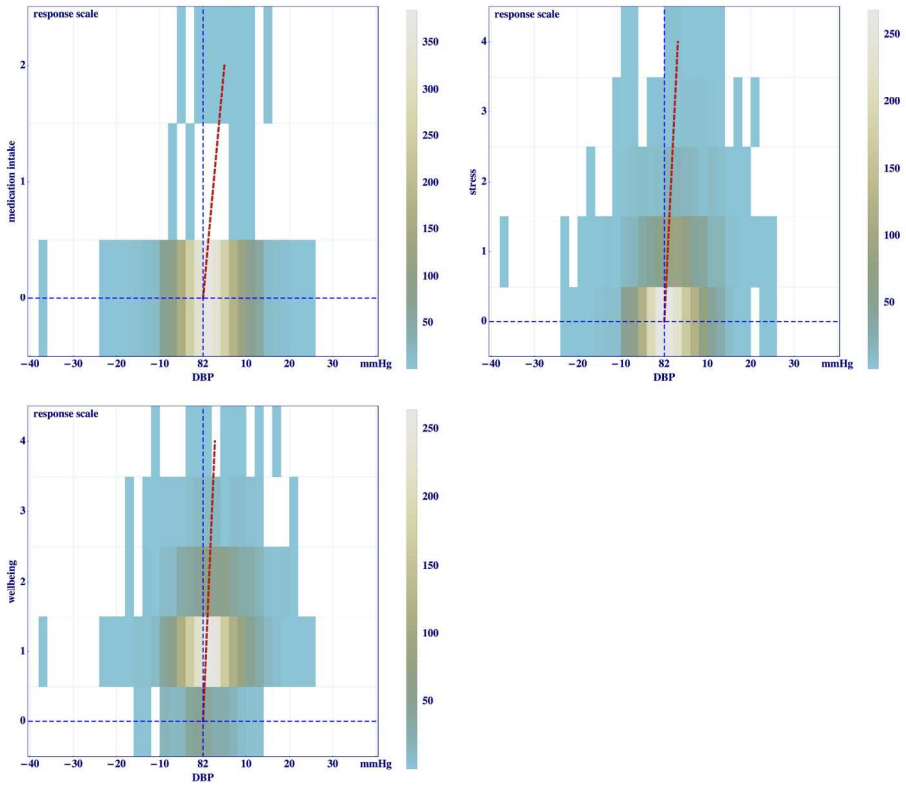

Figures 2a-c Distributions of DBP values by reported level of medication intake (yes-some-no), stress (no-high) and wellbeing (good-poor). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***			Page
	Item No	**Recommendation**	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	23 ref.29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10, 16
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Compl info
		(c) Summarise follow-up time (eg, average and total amount)	Compl info
Outcome data	15*	Report numbers of outcome events or summary measures over time	Compl info

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Links between blood pressure and medication intake, wellbeing, stress, physical activity and symptoms reported via a mobile phone-based self-management support system - a cohort study in primary care

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TITLE PAGE

Title:

Links between blood pressure and medication intake, wellbeing, stress, physical activity and symptoms reported via a mobile phone-based self-management support system – a cohort study in primary care

Authors:

Charles Taft, Associate professor of psychology, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Charles.taft@gu.se

Inger Hallberg, researcher, Department of Medical and Health Sciences, Linköping University, SE-581 83 Linköping, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Inger.hallberg@liu.se

Ulrika Bengtsson, researcher, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Ulrika.bengtsson@gu.se

Karin Manhem, Professor of medicine, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; Department

of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, Karin.manhem@gu.se

Karin Kjellgren, Professor of nursing, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, SE-405 30 Gothenburg, Sweden, Karin.kjellgren@liu.se

Corresponding author: Charles Taft, Charles.taft@gu.se, Tel +46708414845

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ABSTRACT

Objectives

To explore relationships between patients' self-monitoring of blood pressure (BP) and their concurrent self-reports of medication intake, wellbeing stress, physical activity and symptoms.

Design

The study is a secondary analysis of a prospective study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension.

Setting

Four primary health care centers situated in urban and suburban communities in Sweden.

Participants

50 patients undergoing treatment for hypertension.

Primary and Secondary Outcome Measures

Associations between systolic (SBP) and diastolic blood pressure (DBP) and 10 self-report lifestyle-related variables were analyzed using linear mixed-effects modelling.

Results

Medication intake, better wellbeing, less stress and greater physical activity were associated variously with lower same-day SBP and DBP. The single strongest association was found between medication intake and SBP, where failure to take medications was associated with an estimated 7.44 mmHg higher SBP. To a lesser degree, medication intake was also associated with DBP, where DBP was 4.70 mmHg higher in cases where medications were not taken. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated with only SBP. None of the symptoms dizziness, headache, restlessness, fatigue or palpitations were significantly associated with BP.

Conclusions

Our findings that BP was associated with patients' BP management behaviors and experiences of wellbeing and stress but not symptoms suggest that enabling persons with hypertension to monitor and track their BP in relation to medication intake, physical activity, wellbeing, stress and symptoms may be a fruitful way to help them gain first-hand understanding of the importance of adherence and persistence to treatment recommendations.

Trial registration

ClinicalTrials.gov registration number: NCT01510301.

Keywords

Hypertension, self-management, adherence, self-reports, stress, symptoms, wellbeing, physical activity, associations, blood pressure variability

ARTICLE SUMMARY

Strengths and limitations of this study

- The study is unique in investigating associations between self-monitored blood pressure and same-day, self-reported medication intake, wellbeing, stress, physical activity and symptoms during 56 consecutive days
- The mobile phone-based self-management support system was designed in collaboration with patients with hypertension as a tool to enable and empower patients to monitor and track their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module.
- The generalizability of the study results may be impeded by the use of convenience sampling for patient selection.

- The patients reported unusually good medication adherence during the study, suggesting the need to perform larger studies with patients with more diverse adherence levels in order to confirm our findings.

INTRODUCTION

Hypertension is the leading modifiable risk factor for premature death and global disease burden [1, 2]. Reducing hypertension has been shown to lower the risk of acute myocardial infarction, stroke, kidney failure, congestive heart failure and cardiovascular death [3-5]. Despite strong evidence and consensus about the treatment and control of hypertension, [6-9] nonetheless only an estimated 13.8% of adults with hypertension worldwide have their blood pressure (BP) controlled [10].

As in other chronic conditions, successful treatment outcomes in hypertension depend ultimately on effective patient self-management [11, 12, 13]. However, patient adherence to hypertension treatment recommendations is notoriously poor, both with respect to medication taking [14-16] and in particular to lifestyle changes [17-19], underlining the need for supporting patients in their self-management efforts. To date, interventions aimed at supporting self-management have focused mainly on self-monitoring of BP (SMBP), educational programs, and counselling [20]. SMBP has been found to contribute to improved BP control [21-23] and medication adherence [24]; however, evidence for the independent effects of education and counselling remains weak [20].

It has been suggested that educational interventions have failed because they have not sufficiently understood, acknowledged and addressed patients' lay perspectives on the causation and risks of hypertension [25-27]. Lay beliefs are not always consistent with

biomedical opinion [26], particularly regarding the impact of stress on BP, the experience of BP symptoms, and drug side effects, tolerance and dependency, which may partly explain why patient adherence and persistence rates are poor. For example, many patients believe that stress is the main cause of hypertension and that headache, palpitations and dizziness are caused by high BP, and hence patients may cease to adhere to treatment during periods of low stress or in the absence of symptoms [25]. On the other hand, SMBP may improve medication adherence by providing direct feedback on BP levels, independent of experienced symptoms, and thereby contribute to BP control by reinforcing behaviors that lower BP [28].

This study is part of a research program aimed at developing and evaluating a mobile phone-based self-management system to support hypertension self-management. Recently we reported significant BP improvements with the use of the system [29]. Designed in accordance with patients' expressed wishes and perceived needs for support in self-managing hypertension [30-32], the system was hence developed as a tool to enable and empower patients to explore and track variations in their BP in relation to self-reported stress, physical activity, wellbeing, symptoms, and medication intake with a web-based dashboard feedback module. In follow-up interviews, patients indicated that the system helped them to gain insight into the importance of adhering to treatment advice and thereby gain control in managing their condition [33]. However, the usefulness of the feedback module rests on the existence of perceptible links between BP and patient self-reports. A person-centered perspective that emphasizes the value of the patient's own experiences of BP by increased participation in care, self-reporting and documentation has earlier been shown to be beneficial [33]. The purpose of the present study was to explore relationships between patients' SMBP and their concurrent self-reports of stress, physical activity, wellbeing, symptoms, and medication intake.

METHODS

This study was a secondary analysis of a prospective cohort study exploring the 8-week effectiveness of a mobile phone based self-management support system for patients with hypertension. The study took place between February and June 2012 and was approved by the Regional Ethics Board in Gothenburg, Sweden (study code 551-09 and T-100-12), conducted in accordance with the Declaration of Helsinki and registered in the Clinical Trial Protocol Registration System (ClinicalTrials.gov NCT01510301) under the acronym MIHM (Mobile phone In Hypertension Management).

Recruitment and participants

Participants were recruited using convenience sampling. Sample size was estimated for the original study [29] based on a standard deviation (SD) of 12 for systolic BP (SBP) and 7 for diastolic BP (DBP). For detecting a difference of 8 mmHg SBP and 5 mmHg DBP with 90% power and at a 5% significance level, the sample size was estimated to 50 patients. Seventy-three consecutive patients undergoing treatment for hypertension at four primary health care centers in southern Sweden were asked to participate. Inclusion criteria were: currently being medically treated for hypertension, age ≥ 30 years, ability to understand and read Swedish, access to a mobile phone with an internet connection. Eligible patients were informed about the study orally and in writing, and were ensured confidentiality before giving their written informed consent. In total, 54 patients agreed to participate, of whom 3 withdrew before study start.

Patient involvement

Patients with hypertension were involved in all phases of the design, development and evaluation of the mobile-phone based self-management support system. The research question for this study was generated from patient interviews [33] and its merits were confirmed in interviews with professionals. Patients were not involved in drafting the paper. As previously reported [30-33], the system was designed based on interviews in which patients were asked to describe what they needed to better self-manage their hypertension; iteratively developed in collaboration with patients, researchers and clinicians [30-32]; evaluated for content validity, reliability and usability in focus group interviews, cognitive interviews and piloting [32]; examined regarding usability and usefulness in individual patient interviews [33]

The intervention

The interactive self-management support system

As previously described in detail, the system includes four components that have not previously been integrated into the same intervention for supporting self-management of hypertension [29]: 1) a module for self-reporting wellbeing, symptoms, lifestyle, medication intake and side effects of medication; 2) daily home BP and pulse measurements with a validated BP monitor; 3) tailored weekly motivational messages to encourage lifestyle changes and; 4) web-based dashboard to enable patients, as well as physicians and nurses, to examine the patient´s BP in relation to the self-reports. The communication platform for the system was developed by Circadian Questions (CQ), 21st Century Mobile [http://www.cqmobil.se].

Study procedures

Participants were instructed how to use the self-management system and BP monitors by research nurses. They were requested to perform BP measurements and self-reports every evening for eight consecutive weeks and to answer self-report items first and then to measure their BP. The reporting system was open in the evenings between 5 pm and 11 pm and reminders were sent at 7 pm. The actual order in which these two tasks were performed could not be determined from the database, although in the report interface the items were provided first, after which space for BP registration was given. In subsequent interviews participants confirmed that they followed the instructed order [33]. The data reported in through the participants' mobile phones were automatically registered in a secure database.

The system was tailored to the individual patients, such that drug side-effects items (delivered maximum twice weekly) were selected based on the patient's antihypertensive medication; use and choice of motivational messages (delivered maximum twice weekly) were based on patients' preferences; and use of daily reminders was optional.

Patient self-reports

Development and evaluation of the items comprising the self-report module are described in detail elsewhere [31, 32]. Briefly, items were iteratively developed from analyses of patient and professionals (physicians, nurses, pharmacists) focus group interviews about what they considered helpful for supporting self-management of their BP. Six major areas represented by 16 items were identified: three biomedical markers (SBP, DBP and pulse); three symptoms (dizziness, headache and palpitations); four medication side-effects (swollen ankles, dryness of mouth, dry cough and micturition); five quality of life variables (general well-being, stress, restlessness, sleep and fatigue); adherence to medication (medication intake); and one lifestyle variable physical activity. Items were formulated as questions, with "today" as the timeframe. Patients rated items against five-step response scales with anchors not at all (0) - extremely

(4) or very bad (0) - very well/good (4), except medication intake ("Have you taken your medication today?") which was rated on a three-step scale with options yes (0), some of it (1) and no (2) and wellbeing with an inverse five-step scale from very good (0) to very bad (4) (see Supplementary table 1). Blood pressure and pulse were measured and registered as values obtained from BP monitors.

Blood pressure self-monitoring

Patients were instructed how to measure their BP in accordance with the European Society of Hypertension Practice guidelines for home blood pressure monitoring (HBPM) [34]. A home blood-pressure monitor (BP A200 AFIB; Microlife USA Inc., Clearwater, FL, USA) was used and validated according to the international protocol of the European Society of Hypertension [35].

Data analysis

Descriptive statistics were used to characterize patient demographic and clinical variables. Repeated measures linear mixed-effects modeling was used, with SBP and DBP as dependent variables. The variance/covariance structure was specified as autoregressive to guard against violations to sphericity assumptions. All models included a random intercept. Models for the two dependent variables included all 10 self-report variables, excluding medication side-effect variables, as fixed effects. Side-effect variables were excluded because they were assessed only biweekly. Individuals with partial missing data but with at least one observation for each of the independent variables were included. As customary in similar blood pressure studies, day one of the study was excluded from analyses due to abnormally high blood pressure values, hence 55 days were analyzed. Statistical significance was set to p-value < 0.05

throughout. Analyses were performed with SPSS version 22 for Windows, Chicago, IL, USA and Mathematica version 11.0 for Mac (Wolfram Research, Champaign, IL, USA).

RESULTS

Patient characteristics, co-morbidity and medication are shown in Table 1. Of the 51 recruited patients who started the study, one participated only sporadically during the first weeks and dropped out entirely after four weeks and was therefore excluded from the analyses. More men than women took part, as is common in the middle-aged, and other demographics were also comparable with the general hypertensive population in Sweden [36]. The self-reported BP data were validated against the BP values saved in the BP monitor. Among 14 consecutive patients selected for comparison [33], only 21 values of 1448 of both SBP and DBP differed.

Table 1. Patient characteristics (n=50)

Females n (%)	24 (48%)
Mean age (range)	59.5 (33-81)
Mean SBP (range), mmHg[a]	142 (115-195)
Mean DBP (range), mmHg[a]	84 (61-113)
Mean years with hypertension (range)	8.5 (< 1 – 32)
Co-morbidity n, (%)[b]	22 (52)
Co-morbidities n (%):	
Cardiovascular disease	3 (14)
Decreased renal function	2 (9)
Diabetes	7 (32)
Musculoskeletal disorder	3 (14)

Other	7	(32)
Type of antihypertensive medication, n.		
Diuretics	12	
Potassium-sparing diuretics	4	
β-blockers	18	
Calcium channel blockers	22	
ACE inhibitors	11	
Angiotensin II receptor antagonists	21	
ACE inhibitors+diuretic	1	
Angiotensin II receptor antagonist+diuretic	5	
Number of antihypertensive medications, n.		
One	19	
Two	19	
Three	11	
Four	1	
Marital status		
Married	39	(78)
Unmarried	10	(20)
Widow / widower	1	(2)
Education, n (%)		
Compulsory school (≤ 9 years)	5	(10)
High school (9-12 years)	22	(44)
University	22	(44)
Missing	1	(2)
Employment status, n (%)		
Employed	28	(56)

Long-term sick leave	1	(2)
Retired	19	(38)
Missing	2	(4)

[a] Mean of patients' 3-4 baseline BP measurements

[b] Information provided by patients

Of the potential 2750 observations per variable (50 patients*55 days) the average number of observations was 2475 (range=2473-2478), or about 10% missing. Missing data were clustered to a few participants and primarily over sustained periods of a few days. In follow-up interviews, reported partly in Hallberg I. et al. [33], participants explained that reasons for non-reporting were primarily due to poor internet connections during visits to their countryside vacation homes or to inconvenience, unavailability and/or costs associated with internet use during trips abroad. There were only 22 reported instances of partial or nonadherence and these were spread over 11 individuals, or roughly 2 times/ individual during the 55-day study period.

Links between systolic blood pressure and self-report variables

Mixed models analysis, including all 10 independent variables, yielded significant associations between SBP and medication intake, physical activity, wellbeing and stress (Table 2). Self-reported medication intake was associated with the largest decrease in SBP, where better adherence was associated with a 3.72 mmHg decrease in SBP per reported adherence level. SBP increased 1.09 mmHg with increasing levels of stress, 1.51 mmHg with decreasing levels of wellbeing and 0.70 mmHg with decreasing levels of physical activity. Figures 1a-d show the distribution of SBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 2. Linear mixed-effect model for associations between systolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	134.40	1.93	63.14	69.57	.000	130.54-138.26
Medication intake	3.72	1.19	2311.12	3.13	.002	1.39-6.04
Physical activity	-.70	.22	2274.21	-3.14	.002	-1.13--.26
Wellbeing	-1.51	.47	2407.81	-3.23	.001	-.59--2.42
Stress	1.09	.36	2400.96	3.04	.002	.39-1.80
Headache	.52	.46	2389.47	1.14	.253	-.37-1.41
Sleep	.57	.29	2208.24	1.95	.052	-.00-1.15
Dizziness	-.69	.65	2381.66	-1.05	.293	-1.97-.59
Palpitation	-.14	.57	2406.14	-.24	.808	-1.25-.98
Fatigue	-.32	.33	2364.10	-.98	.328	-.96-.32
Restless	.88	.55	2403.86	1.59	.113	-.21-1.96

Figure panels 1a-d about here

Links between diastolic blood pressure and self-report variables

A model including all 10 self-report variables showed significant associations between medication intake, wellbeing and stress (Table 3). Self-reported medication intake was associated with the largest decrease in DBP, where better adherence was associated with a 2.35 mmHg decrease in DBP per reported adherence level. Higher levels of stress and poorer wellbeing were associated with small DBP increases (0.81, 0.70 mmHg/ scale step, respectively). Figures 2a-c show the distribution of DBP in relation to patient ratings along with regression lines for each of the significant self-reported variables.

Table 3. Linear mixed-effect model for associations between diastolic blood pressure and self-report variables

Variable	Estimate	Std. Error	df	t	Sig.	95% CI
Intercept	78.44	1.00	69.14	78.43	.000	76.44-80.43
Medication intake	2.35	.71	2326.88	3.31	.001	.96-3.77
Physical activity	-.11	.13	2300.01	-.79	.428	-.37-.15
Wellbeing	-.70	.28	2411.21	-2.51	.012	-.15--1.24
Stress	.81	.22	2404.96	3.79	.000	.39-1.23
Headache	.52	.27	2383.25	1.92	.055	-.01-1.05
Sleep	.30	.18	2239.18	1.69	.090	-.05-.64
Dizziness	-.60	.39	2390.90	-1.52	.128	-1.36-.17
Palpitations	.11	.34	2415.45	.32	.746	-.55-.77
Fatigue	-.178	.20	2383.60	-.88	.381	-.55-.21
Restless	.28	.33	2408.78	.85	.395	-.37-.93

Figure panels 2a-c about here

DISCUSSION

Our results showed that patient self-reports of medication intake, wellbeing, stress and physical activity were associated variously with same-day SBP and DBP. The single strongest association was found between medication intake and SBP, where failure to take medications was associated with a cumulative increase in SBP of 7.44 mmHg . To a lesser degree, medication intake was also associated with DBP, where DBP was 4.70 mmHg higher in cases where medications were not taken. Wellbeing and stress were consistently associated with SBP and DBP, whereas physical activity was associated only with SBP. None of the assessed symptoms (dizziness, headache, wellbeing, fatigue and palpitations) were significantly associated with BP, although a near significant association was seen between headache and DBP.

To our knowledge this is the first study to report independent effects of self-reported non-adherence to medication on same-day BP. Our results, particularly regarding SBP, corroborate and extend longer-term BP effects reported by, for example, Rose et al. [37] that week-long periods of poor adherence are associated with about 12-15/7-8 mmHg higher BP than good adherence, by Hedna et al. [38] that non-adherence during a one-month period is associated with higher odds of elevated BP, as well as earlier studies showing longer term effects of non-adherence on BP control [39, 40]. We also have analyzed the effects of using the mobile phone system over eight-weeks and found significant decreases in SBP (-7 mmHg)

and DBP (-4.9 mmHg) [29]. Our findings of same-day associations may potentially be exploited in SMBP-based self-management programs to help hypertensives gain an understanding of the immediate impact of hypertensive medication on BP and thereby reinforce medication adherence and persistence. However, caution should be observed in interpreting our results given that few instances of partial or nonadherence were reported over the course of the 8-week study period and the missing data rate was 10%.

Self-reported wellbeing and stress were significantly associated with same-day BP. Again, stronger effects were seen in relation to SBP, where SBP was an estimated 4.53 mmHg higher when wellbeing was rated poor than when rated good and 3.27 mmHg higher when stress was high versus low. Corresponding DBP values were 2.10 for wellbeing and 2.43 for stress. Our findings corroborate links between BP and subjective wellbeing reported among hypertensive patients with coronary artery disease [41] and lend some support to the lay notion that hypertension is not asymptomatic [25]. Moreover, our findings regarding stress are in line with a large body of research showing strong and consistent associations between stress and increases in BP levels [42, 43]. Although BP spikes associated with acute stress are normal physiological reactions to stressors, chronic stress is acknowledged as an important risk factor for cardiovascular disorders and events. [43]. It may therefore be beneficial to monitor stress levels in connection with SMBP, both to help patients understand the importance of stress avoidance and to help clinicians assess the need for instituting stress reduction therapy.

High levels of self-reported physical activity were associated with moderately lower levels of same-day SBP (-2.10 mmHg). This finding was not unexpected given that BP-mitigating effects of physical activity are yielded after sustained periods of training [44]. Physical activity is a recommended lifestyle modification for the prevention and management of

hypertension [45] and tracking physical activity in relation to BP may help to motivate patients to adhere to this recommendation.

No significant associations were found between symptoms (dizziness, headache and palpitations) and BP, although a near significant association (p=.055) was found between headache and DBP. The lack of associations between symptoms and BP may possibly be due to the fact that patients reported few symptoms during the study period. Nevertheless, our finding is in line with earlier studies indicating a lack of association between elevated BP and symptoms (dizziness, headache and palpitations) [46, 47]. Monitoring symptoms in connection with SMBP may, however, serve to inform patients who base their medication intake on the presence or absence of symptoms [25] that symptom experience is an imperfect indicator of BP levels.

There are a number of limitations to this study. Although the socio-demographic distribution of the sample corresponded to that of the hypertensive population in Sweden [36], the sample was selected using convenience sampling, which has clear-cut implications for the generalizability of our results. The patient sample also reported unusually good medication adherence during the study, where only 11 patients reported any nonadherence (in total 7 reports of partial medication intake and 15 of no medication intake) were reported over the course of the 8-week study period. We cannot preclude that our high adherence rates may owe to sampling, reactivity or social desirability bias. Larger and randomized studies including patients with more diverse adherence levels are needed to confirm our findings.

CONCLUSIONS

Significant same-day associations were evidenced between BP and medication intake, stress, physical activity and wellbeing; however, symptoms that patients often associate with high BP were not associated with BP.

The mobile phone system enables patients to monitor and track BP in relation to patient behaviors and experiences and may have important implications for adherence to treatment recommendations by helping patients gain first-hand insight into the blood pressure lowering effects of medication intake and physical activity, stress avoidance, etc. and inform patients who base adherence decisions on symptom experience that symptoms are poor indicators of blood pressure levels.

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COMPETING INTERESTS

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

TRANSPARENCY DECLARATION

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that discrepancies from the study as planned have been explained.

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DATA SHARING STATEMENT

Patient level data may be obtained by contacting the corresponding author. There are no additional data available for data sharing. Consent for data sharing was not obtained from participants but the presented data are anonymized and risk of identification is low.

CONTRIBUTORS

CT designed the study, performed data analyses, and drafted and revised the paper. He is guarantor. IH designed the study, monitored data collection and revised the paper. UB designed the study, monitored data collection and revised the paper. KM drafted and revised the paper. KK initiated the project, designed the study, and drafted and revised the paper. She is guarantor.

All authors have approved the submitted manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Figure legends

Figures 1a-d. Distributions of SBP values by reported level of medication intake (yes-some-no), stress (no-high), wellbeing (good-poor) and physical activity (no-high). Regression lines for the relationships between SBP and the independent variables are shown in red. Colors denote concentrations of SBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept SBP value (135 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

Figures 2a-c Distributions of DBP values by reported level of medication intake (yes-some-no), stress (no-high) and wellbeing (good-poor). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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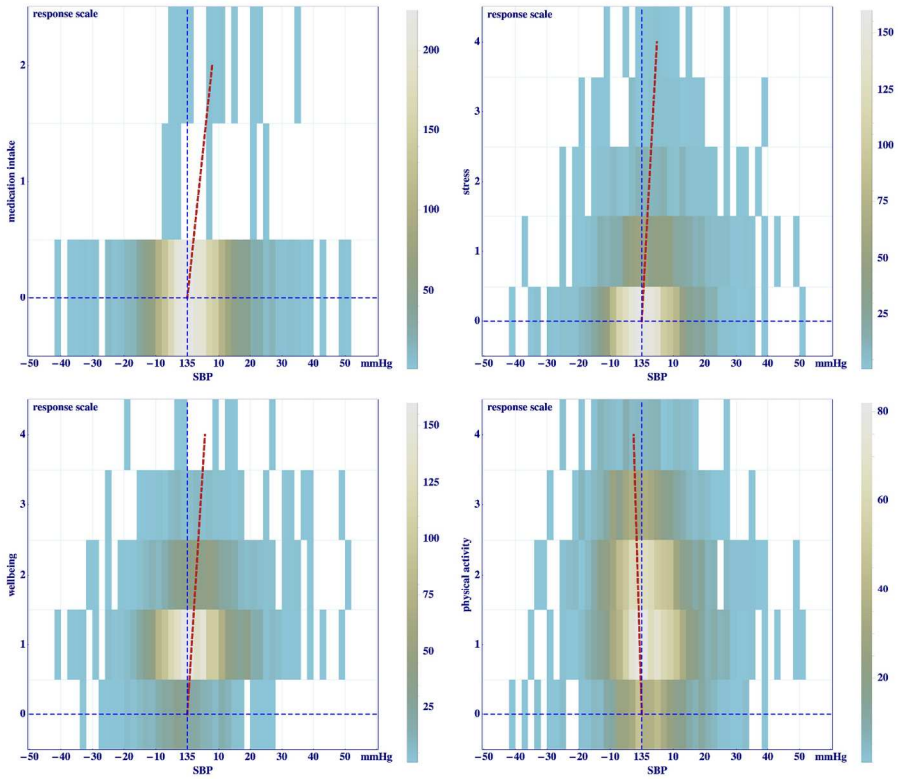

Figures 1a-d. Distributions of SBP values by reported level of medication intake (yes-some-no), stress (no-high), wellbeing (good-poor) and physical activity (no-high). Regression lines for the relationships between SBP and the independent variables are shown in red. Colors denote concentrations of SBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept SBP value (135 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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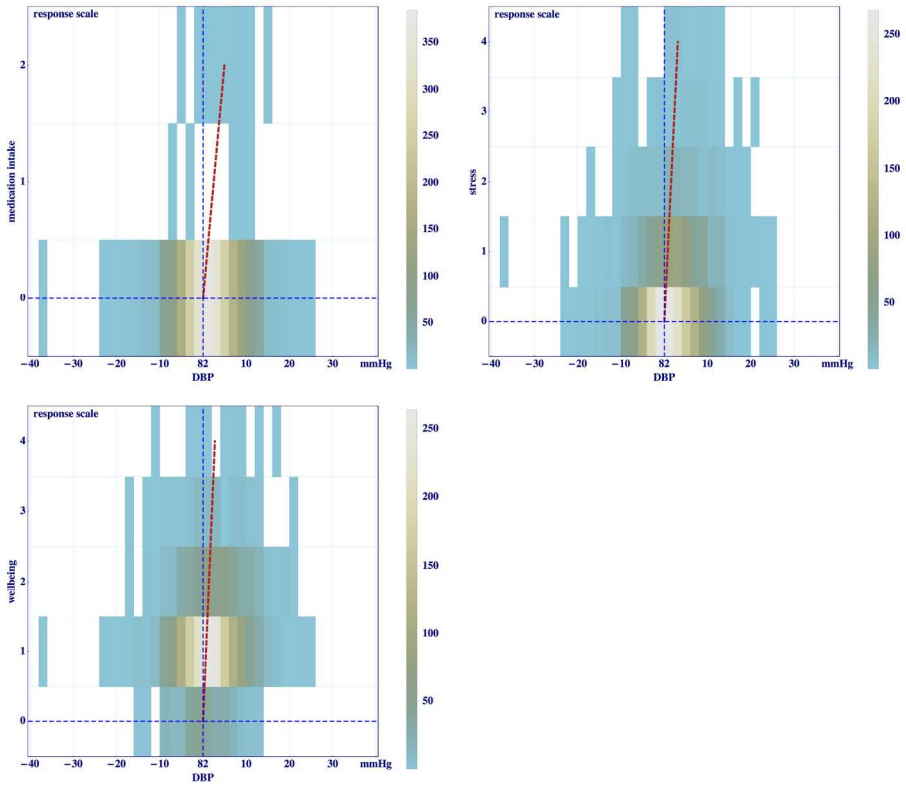

Figures 2a-c Distributions of DBP values by reported level of medication intake (yes-some-no), stress (no-high) and wellbeing (good-poor). Regression lines for the relationships between DBP and the independent variables are shown in red. Colors denote concentrations of DBP values, where light yellow indicates higher concentrations of observations and light blue lower concentrations. The x-axis has been transformed to indicate deviations from the intercept DBP value (82 mmHg). NB: medication intake includes 7 observations where partial medication adherence (1) was reported and 11 observations where medication adherence was reported as none (2).

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Supplementary table 1. Items and response scales.

Items*	**Abbreviated items**	**Response formats (steps)**
What is your systolic blood pressure today?	Systolic BP today?	Value
What is your diastolic blood pressure today?	Diastolic BP today?	Value
What is your pulse today?	Pulse today?	Value
How do you feel today?	How do you feel today?	Good - Bad (5)
Have you taken your blood pressure medicine as prescribed today?	Taken your medicine today?	Yes – Some of it - No (3)
Have you felt tired today?	Tired today?	Not all all - Extremely (5)
Have you felt dizzy today?	Dizzy today?	Not all all - Extremely (5)
Have you had headache today?	Headache today?	Not all all - Extremely (5)
Have you had heart palpitations today?	Heart palpitations today?	Not all all - Extremely (5)
Have you felt restless today?	Restless today?	Not all all - Extremely (5)
How did you sleep last night?	How did you sleep last night?	Bad - Good (5)
Have you been physically active today?	Physically active today?	Not all all - Extremely (5)
Have you felt stressed today?	Felt stressed today?	Not all all - Extremely (5)
Have you had swollen ankles today?**	Swollen ankles today?	Not all all - Extremely (5)
Has your mouth been dry today?**	Dry mouth today?	Not all all - Extremely (5)
Have you had a dry cough today?**	Dry cough today?	Not all all - Extremely (5)
Have you passed water often today?**	Passed water often today?	Not all all - Extremely (5)

*Full questions were presented in participants' instruction booklets and were abbreviated to fit mobile phone displays. Items and response formats are translated from Swedish.

**Drug side-effect questions were asked only when relevant for prescribed medications

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***			Page
	Item No	**Recommendation**	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	23 ref.29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10, 16
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Compl info
		(c) Summarise follow-up time (eg, average and total amount)	Compl info
Outcome data	15*	Report numbers of outcome events or summary measures over time	Compl info

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.