eHealth in hypertension and cardiovascular disease

Opportunities and challenges

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eHealth in hypertension and cardiovascular disease: opportunities and challenges

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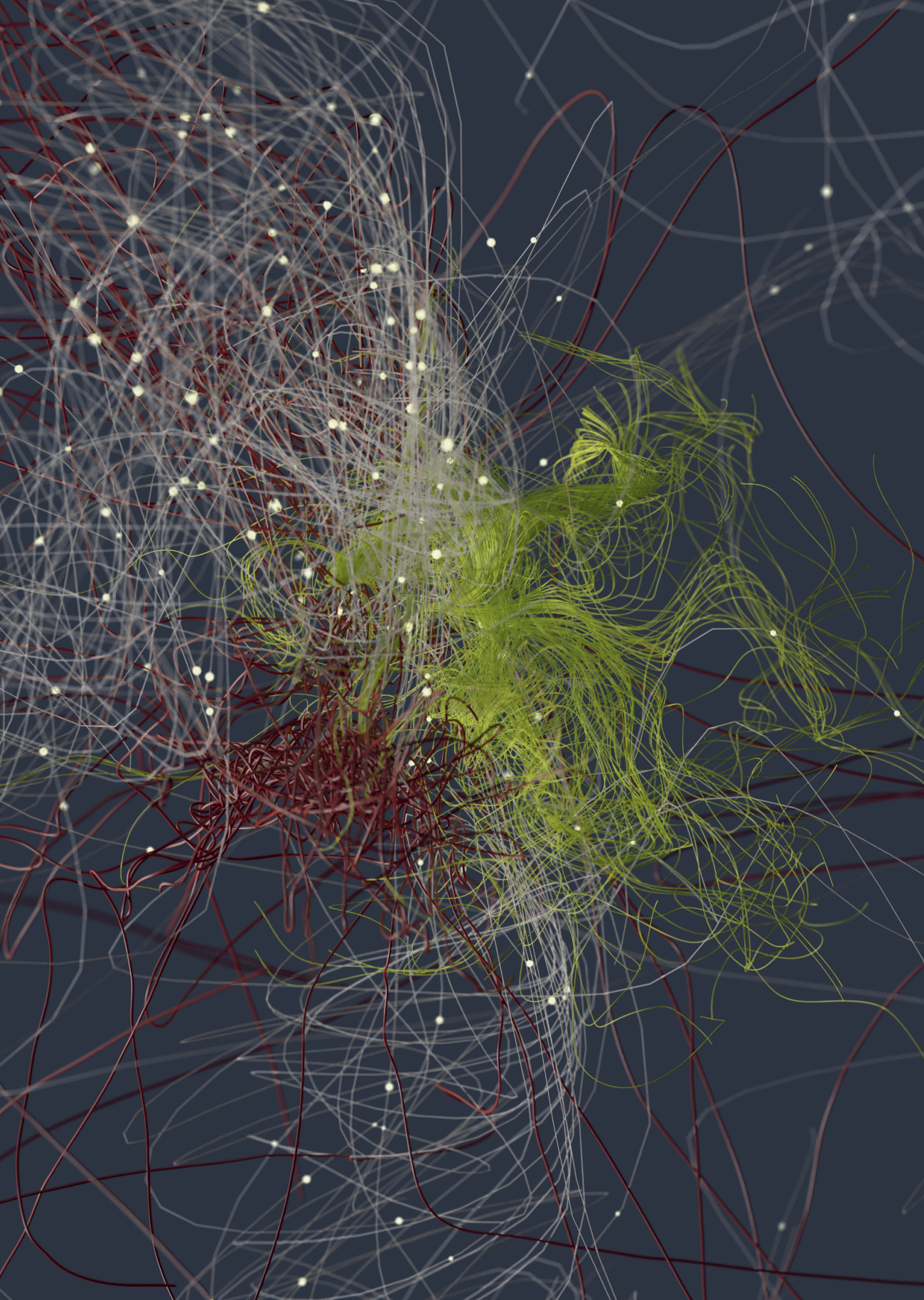
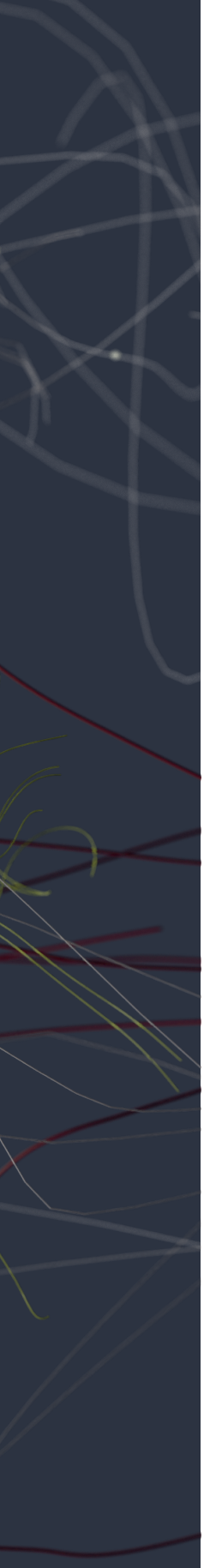




Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Cardiovascular disease and hypertension

Cardiovascular disease is the leading cause of death worldwide, accounting for 20% of the total global burden of disease in women and 24% in men [1]. High blood pressure is the most important modifiable risk factor for cardiovascular disease worldwide [2]. In most high income countries, the number of deaths caused by CVD is reducing because of life saving interventions and improved treatment possibilities, however, the number of hospitalizations for CVD is still increasing. Treatment possibilities for hypertension and its cardiovascular complications have significantly improved over the past decades, transforming it to lifetime chronic disorders rather than leading to acute death [3]. However, treatment of hypertension is still suboptimal and only less than a quarter of individuals with hypertension have their blood pressure controlled [4]. Major factors contributing to the large proportion of hypertension being suboptimally treated and uncontrolled are physician inertia and non-adherence of blood pressure lowering medication, although socio economic status and ethnicity also play an important role [5,6].

Disease management

The number of patients living with chronic cardiovascular disease is a burden for our healthcare system and society. Monitoring and managing cardiovascular risk factors effectively and efficiently, while maintaining the highest possible levels of quality of life is challenging. The digital revolution of our times provides opportunities for large scale measurement, storage, and transfer of health data, such as BP and heart rhythm, that may help clinicians to deal with the CVD endemic. At the same time, concerns on this large scale health data are raised, similar to those with the introduction of blood pressure measurement in the beginning of the 20th century: "*There is a certain risk that the multiplication of instruments tens to pauperize the senses and to weaken their clinical acuity; even the sphygmograph is mainly used nowadays for the purposes of demonstration or of making a permanent record than for what it can tell us in diagnosis or prognosis*"[7]. In other words, as is the case for a single blood pressure measurement executed by a physician, large scale home measurement of health parameters only adds value if combined with adequate interventions if needed.

eHealth

eHealth is defined as the use of information and communication technologies (ICT) for health and compromises for instance mobile health applications, electronic health

records and telemonitoring [8]. The development of a widespread digital infrastructure with our smart mobile devices and the introduction of consumer-focused health devices such as blood pressure monitors and ECG-recorders have paved the way for the uptake of eHealth in clinical daily practice. Specifically for chronic cardiovascular disease, monitoring programs in which patients measure their health themselves while being remotely checked by dedicated healthcare professionals, have been highly anticipated, and over the past decade have seen an increasing interest with more studies on the topic each year [9]. However, evidence on its effectiveness is heterogeneous and concerns on for instance data security, technical accuracy, cost-effectiveness and patients' quality of life have hampered eHealth to live up to its promise [10]. In recent years, the COVID-19 pandemic has pushed adoption of eHealth, while concerns have been raised on its accessibility for individuals with different socioeconomic statuses and ethnic backgrounds [11,12]. The aim of this thesis is to evaluate these challenges and to identify success factors and opportunities, thereby contributing to eHealth finally living up to its potential.

Part of this thesis is centered around the Dutch eHealth program HartWacht, as an example of a successful home monitoring program for hypertension and cardiovascular disease (see Figure 1.1) [13,14]. HartWacht is a dedicated ICT infrastructure that has been developed as a remote telemonitoring program combined with an eHealth application for patients at high CVD risk. Patients participating in this program are diagnosed with cardiac arrhythmias, chronic heart failure or difficult to treat hypertension, and are provided with home measurement devices to record blood pressure, weight and/or ECGs. Patients are instructed to perform measurements according to protocol, in fixed frequency or symptom-driven. Data are stored locally on the smart device owned by a patient and in the online accessible patient file. Meaurements are automatically classified as normal or deviating by algorithms, of which the result is instantly available for the patient. The health data is incorporated in the Electronic Health Record of the patient and remotely assessed according to protocols by the Hartwacht team, consisting of health professionals supervised by a medical specialist with 24/7 availability. The team can remotely contact the patient if needed, for instance to request for another measurement or instructions about medication. When home measurements are structurally deviating and additional diagnostics are necessary, the patient receives regular outpatient care.

For the HartWacht program to be successful, the concerns as described earlier should be taken into consideration and the pitfalls should be avoided. Remote monitoring eHealth programs need to be accessible, especially for populations at increased risk for cardiovascular disease. The program should be reliable and functional and as

data is gathered outside of the hospital, data security and patient privacy should be guaranteed. For the program to be scalable and affordable, data-handling should be optimized and automized. Simultaneously, especially where healthcare delivery is partially automized, patient experience is key. Participants of the HartWacht program should experience at least equivalent levels of quality of life as compared to patients receiving usual care, and clinical outcomes should be better.

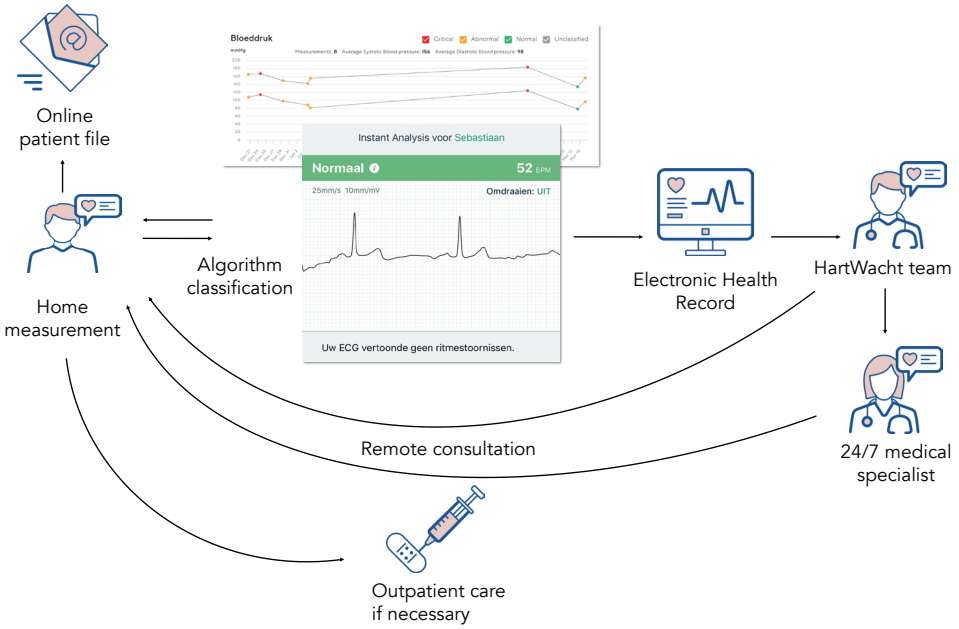


Figure 1.1: The remote monitoring infrastructure of HartWacht (Cardiologie Centra Nederland). Self-measurements by patients are stored in their online patient files and directly classified by algorithms. Data is presented in a dashboard in the electronic health record where it is assessed by the HartWacht team, supervised by a medical specialist with 24/7 availability. If needed, the team can remotely consult with the patients and provide additional outpatient care.

THESIS OUTLINE

Thorough understanding of the target populations and factors influencing hypertension is essential in developing new disease management strategies such as eHealth remote monitoring programs. In **chapter 2** we therefore provide an overview of hypertension in different ethnic groups in Amsterdam, the Netherlands, and we show how the association between socioeconomic status and its prevalence, awareness, treatment and control differs between those groups.

In the following chapters we present challenges that accompany eHealth implementation, in each chapter followed by potential solutions and opportunities. In **chapter 3** we evaluate the heterogeneity in evidence on cost-effectiveness of eHealth programs and distill three success factors based on a meta-analysis. In **chapter 4** we address the concerns about data-security in remote monitoring programs and provide a roadmap on how to set up an eHealth infrastructure compliant with EU privacy regulations. In **chapter 5** we analyze the accuracy of a novel technology for heartbeat detection and show that its performance is sufficient for future potential use in bracelets and smartwatches for eHealth programs for cardiac arrhythmias. In **chapter 6** we evaluate the large amount of data that is collected in eHealth programs propose an optimized framework for automized data handling to decrease risk of alarm fatigue.

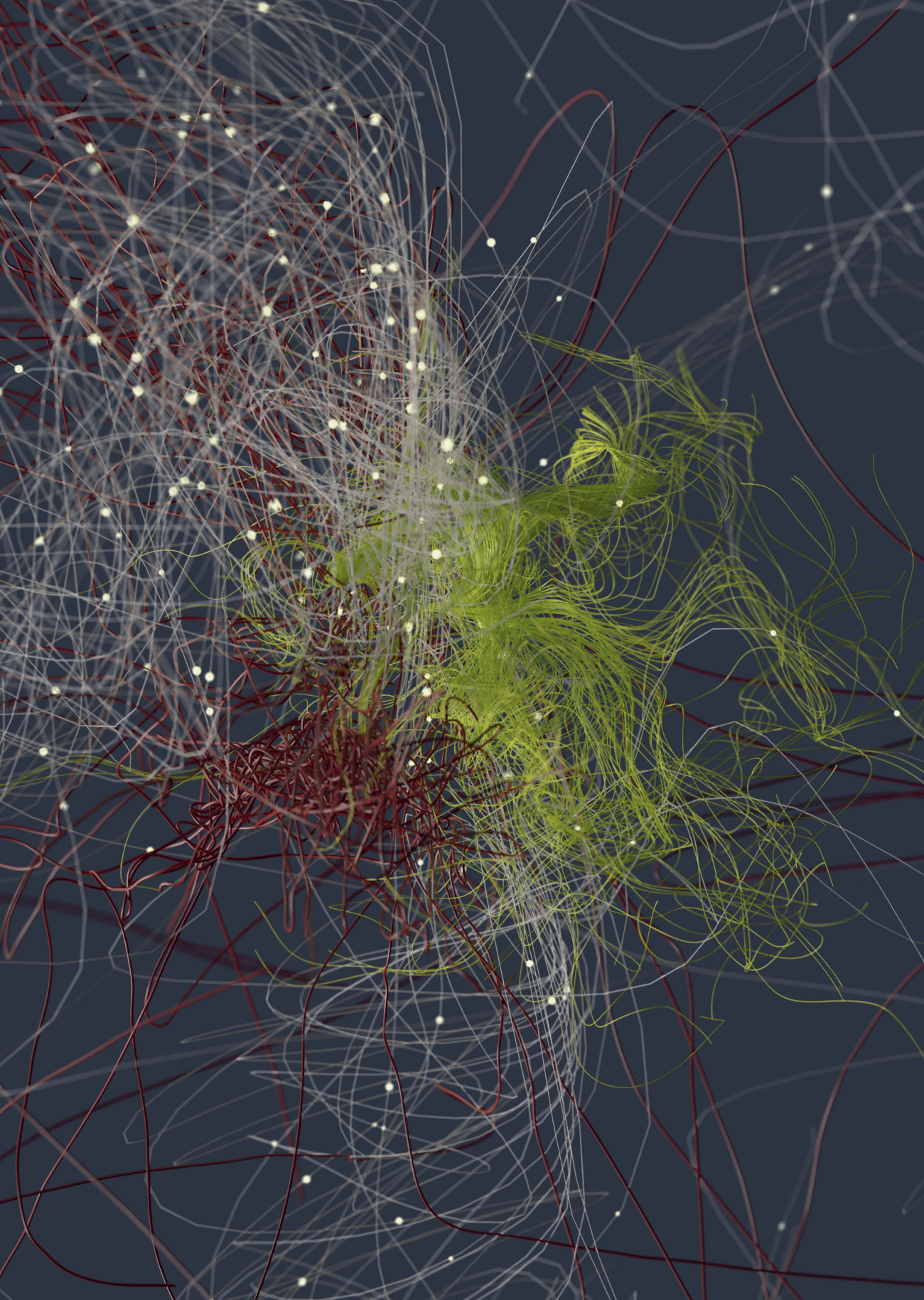
We then zoom in on the patients: in **chapter 7** we investigate how participating in a remote monitoring program impacts quality of life, and in **chapter 8** we identify patient characteristics that potentially contribute to successful eHealth participation. We additionally describe the rationale, design and cohort profile of the Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (EMPATHY) trial in which we investigate the effectiveness of the HartWacht program.

In **chapter 9** we observe how the COVID pandemic increased interest in and urgency for remote solutions and show how it directly affected the uptake of eHealth in general practices in the Netherlands.

REFERENCES

1. Thomas H, Diamond J, Vieco A, et al. Global Atlas of Cardiovascular Disease 2000-2016: The Path to Prevention and Control. *Glob Heart* 2018; 13: 143.
2. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet* 2016; 388: 2665–2712.
3. Timmis A, Townsend N, Gale CP, et al. European society of cardiology: Cardiovascular disease statistics 2019. *Eur Heart J* 2020; 41: 12–85.
4. Blok S, Haggenburg S, Collard D, et al. The association between socioeconomic status and prevalence, awareness, treatment and control of hypertension in different ethnic groups. *J Hypertens*; Publish Ah. Epub ahead of print 19 January 2022. DOI: 10.1097/HJH.0000000000003092.
5. Faria C, Wenzel M, Lee KW, et al. A narrative review of clinical inertia: focus on hypertension. *J Am Soc Hypertens* 2009; 3: 267–276.
6. Burnier M, Egan BM. Adherence in Hypertension. *Circ Res* 2019; 124: 1124–1140.
7. Allbutt TC. The Prevention of Apoplexy. *Bristol Med Chir J* (1883) 1905; 23: 1–10.

8. World Health Organisation. WHO - Global Observatory for eHealth, https://www.who.int/observatories/global-observatory-for-ehealth (accessed 26 February 2022).
9. Boogerd EA, Arts T, Engelen LJ, et al. "What Is eHealth": Time for An Update? *JMIR Res Protoc* 2015; 4: e29.
10. Schreiweis B, Pobiruchin M, Strotbaum V, et al. Barriers and Facilitators to the Implementation of eHealth Services: Systematic Literature Analysis. *J Med Internet Res* 2019; 21: e14197.
11. Guo Z, Zhao SZ, Guo N, et al. Socioeconomic Disparities in eHealth Literacy and Preventive Behaviors During the COVID-19 Pandemic in Hong Kong: Cross-sectional Study. *J Med Internet Res* 2021; 23: e24577.
12. Reiners F, Sturm J, Bouw LJW, et al. Sociodemographic factors influencing the use of ehealth in people with chronic diseases. *Int J Environ Res Public Health*; 16. Epub ahead of print 2019. DOI: 10.3390/ijerph16040645.
13. Kolk MZH, Blok S, De Wildt MCC, et al. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal*. Epub ahead of print 9 March 2021. DOI: 10.1093/ehjdh/ztab030.
14. Wierda E, Blok S, Somsen GA, et al. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of Hartwacht as a learning case. *BMJ Innov* 2020; 6: 170–176.



Chapter 2

The association between socioeconomic status and prevalence, awareness, treatment and control of hypertension in different ethnic groups: the HELIUS study

Sebastiaan Blok, Sabine Haggenburg, Didier Collard, Eva L. Van der Linden, Henrike Galenkamp, Eric P. Moll Van Charante, Charles Agyemang, Bert-Jan H. van den Born

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ABSTRACT

Background: Socioeconomic status (SES) and ethnicity are both important determinants of hypertension prevalence and control rates, but their separate contribution is unknown. We assessed the association of SES with hypertension prevalence, awareness, treatment and control and whether this differs between ethnic groups.

Methods: We used baseline data from the Healthy Life in an Urban Setting (HELIUS) study, a multi-ethnic population-based cohort study, including 18,106 participants (84% of the total cohort) of Dutch (n = 4,262), African Surinamese (n = 3,732), Moroccan (n = 2,902), Turkish (n = 2,694), South-Asian Surinamese (n = 2,664) and Ghanaian (n = 1,947) descent with data on SES and hypertension status.

Results: Regardless of ethnicity, lower SES was associated with higher hypertension prevalence, especially in participants with no education compared to those with higher levels of education (OR 2.29 [2.05-2.56]). There was an inverse association between SES and hypertension treatment with the strongest association for lower compared to higher educated participants (OR 1.63 [1.39-1.90]). In addition, lower SES was associated with lower hypertension control with the strongest association for participants with the lowest compared to the highest occupational level (OR 0.76 [0.60-0.95]). The association between educational level and treatment, but not the other SES- or hypertension-indicators, was influenced by ethnicity, with lower educated Dutch and African Surinamese having higher ORs for hypertensive treatment (Dutch OR 1.98 [1.43-2.76]; African Surinamese OR 1.44 [1.10-1.89]).

Conclusion: SES, in particular education, impacts hypertension treatment in the Netherlands, while the association of specific SES-parameters with hypertension indicators differ across ethnic groups. Further exploration is needed on how socio-cultural beliefs and behaviours may differentially affect blood pressure control across ethnic minority populations.

BACKGROUND

Worldwide around 17 million deaths are caused by cardiovascular disease (CVD) each year [1]. Early detection, treatment and control of hypertension significantly reduces the risk of CVD, but despite the availability of guidelines and cheap and effective treatment, in a large number of patients hypertension remains undetected, untreated or inadequately controlled [2,3].

In high-income countries, socioeconomic status ((SES) is positively associated with health [4]. It is hypothesized that socioeconomic disadvantage leads to lower access to care, lower health literacy or diminished ability to pursue a healthy lifestyle [2,3]. For migrant populations from low- and middle-income countries residing in high-income countries, the association of SES with hypertension has not been well established [5]. Limited evidence is available about the association of SES with awareness, treatment and control of hypertension especially for migrant groups [3]. It has been shown that prevalence of hypertension is higher in ethnic minority groups in Europe [5–8], and that hypertension is more frequently uncontrolled compared with the host European populations [5,9,10]. This implies that ethnicity is an important factor to consider in hypertension management. The reasons for inequalities in hypertension prevalence among people with different ethnicities are still unclear, although migration-related lifestyle changes, aging and genetic predispositions have been suggested as potential underlying factors [5,10]. Since ethnic minority groups in high-income countries mostly have lower SES [11], this may contribute to previously reported higher hypertension prevalence rates and lower control rates. Therefore, our aim was to investigate the association of SES with hypertension prevalence, awareness, treatment and control in a multi-ethnic population and assess whether this association is similar for different ethnic groups.

DATA AND METHODS

Study population

For this research, baseline data from the Healthy Life in an Urban Setting (HELIUS) study was used. The rationale, conceptual framework, design and methodology of the HELIUS study have been described elsewhere [12,13]. In brief, HELIUS is a multi-ethnic population-based cohort study that has been set up to investigate health and healthcare utilization among the six major ethnic groups in Amsterdam, The Netherlands. Participants were randomly selected from the municipal registers of Amsterdam, with

stratified sampling for different ethnic groups to allow for comparable group sizes. Baseline data collection took place between January 2011 and June 2015. Participants were aged 18-70 years old at examination and were from African Surinamese, South-Asian Surinamese, Turkish, Moroccan, Ghanaian and Dutch ethnic origin. The study protocols were approved by the Institutional Review Board of the Amsterdam University Medical Centre at the University of Amsterdam. All participants provided written informed consent prior to study enrolment.

Definitions and measurements

The data were collected by standardized questionnaires and physical examination. During physical examination biological samples were obtained.

Ethnicity was defined according to the registered country of birth as well as that of the participants parents. Participants were considered as non-Dutch ethnic originated if either of the following criteria were fulfilled: being born outside of the Netherlands with at least one of his/her parents born abroad (first generation migrant); or being born in the Netherlands, but both parents were born abroad (second generation migrants). The selected ethnicities were chosen as they comprise the largest ethnic minority groups in Amsterdam, where 35% of inhabitants have a non-Western origin [14]. Based on their migration background, which traces back to West-Africa (Ghanaians and African-Surinamese), Northern India (South-Asian Surinamese), Morocco and Turkey they are among the main ethnic minority groups in Europe originating from outside of the European Union. Participants of Surinamese ethnic origin were further classified according to self-reported ethnic origin (obtained by questionnaire) into 'African', 'South-Asian' or 'other' [13].

Individuals were classified as hypertensive if their systolic blood pressure (SBP) was ≥ 140 mmHg or diastolic blood pressure (DBP) was ≥ 90 mmHg at time of physical examination [15], or if they reported use of antihypertensive medication. Blood pressure (BP) was measured in duplicate using a validated automated digital BP device (Microlife WatchBP Home, Microlife AG, Heerbrugg, Switzerland) on the left arm in a seated position after the subject had been seated for at least 5 min, and the mean of the two measurements was used in the analyses [5]. Following previous research, we defined awareness of hypertension as all participants with hypertension during physical examination that self-reported any prior diagnosis of hypertension by a health-care professional [5]. Treatment of hypertension was defined as the proportion of hypertensive participants that reported receiving prescribed antihypertensive

medication for management of elevated blood pressure at time of the interview. Hypertension control was defined as the proportion of hypertensives on self-reported antihypertensive medication with SBP < 140 mmHg and DBP < 90 mmHg at time of physical examination. Cardiovascular disease was defined as self-reported hospital admission for stroke, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft.

We used educational level, occupational status and occupational level as indicators of SES. Educational level was based on the highest qualification attained in the Netherlands or in the country of origin and was classified into four categories: 1. Never been to school or elementary school; 2. Lower vocational schooling or lower secondary schooling; 3. Intermediate vocational schooling or intermediate or higher secondary schooling; 4. Higher vocational schooling or university (e.g. post-secondary schooling or university of applied sciences). Occupational status was chosen to be one of the indicators, to compare people in and outside the working environment. Occupational status was classified into the following four categories: 1. Employed; 2. Not in working population (retirees, housemaker, students or schooling people); 3. Unemployed; and 4. Unfit for work (incapacitated). Occupational level was classified according to the Dutch Standard Occupational Classification system [16], which provides an extensive systematic list of all professions in the Netherlands, and consisted of five categories, based on job title and job description, including a question on fulfilling an executive role. The categories were classified as follows: 1. Elementary occupations; 2. Lower occupations; 3. Middle or secondary occupations; 4. Higher occupations; 5. Scientific occupations. In this study, because of small number of participants in the latter two groups, we combined the categories higher and scientific occupations to form one category.

Selection of participants

For the present study we used the data of all individuals with available information on SBP and DBP and antihypertensive medication at time of physical examination (n = 22,112). We excluded all participants with unknown or other ethnic origin (n = 547) and excluded an additional 3,459 participants with missing data on SES indicators, leaving 18,106 participants for analysis (Figure 2.1). We chose to perform analysis on this smaller dataset to prevent indistinctive comparisons, and the remaining number of participants in each subgroup in the cohort was still large. Compared to those with complete cases, participants with missing SES data were comparable in age and sex, and prevalence of hypertension, but were more frequently of Ghanaian,

Turkish or Moroccan origin and were more likely to have a lower level of education (Supplemental Data File 2.1). This resulting dataset consisted of 4,262 Dutch, 3,732 African Surinamese, 2,802 Moroccans, 2,699 Turkish, 2,664 South-Asian Surinamese, and 1,947 Ghanaians. For the analysis on occupational status, we excluded participants outside of the working population (e.g. retirees, homemakers and students) because of large heterogeneity in age in this subgroup (n = 2,082). An overview of characteristics of all participants stratified by occupational status are described in Supplemental Data File 2.2. Compared to those employed, unemployed and unfit for work, participants not in the working population were more likely woman, had a median higher age and had previously worked on a lower occupational level.

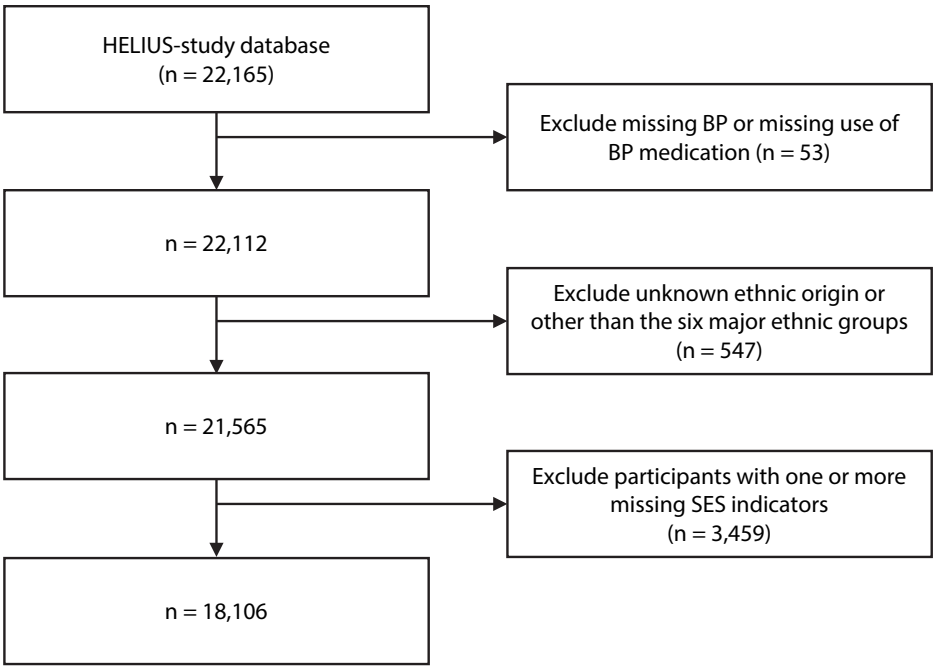

Figure 2.1: Flow diagram of selection of participants.

Statistical analysis

Baseline characteristics of the study populations were presented separately for each ethnic group with mean and standard deviation for normally and median with interquartile range non-normally distributed continuous variables, and as number with percentage for categorical variables. Logistic regression analyses were performed to study associations between every SES indicator and hypertension prevalence,

awareness, treatment and control, with and without adjustment for covariates with known association to hypertension. Throughout all analyses we adjusted for age and sex in model 1. In model 2, we adjusted for age, sex and ethnicity. In model 3 we additionally adjusted for body mass index (BMI, weight in kilograms divided by length in meters squared (kg/m^2)) and diabetes (defined by a fasting plasma glucose level ≥ 7.0 mmol/L, self-reported diabetes, or treatment with glucose-lowering medication). In the final model (model 4) we additionally adjusted for history of cardiovascular disease. To study the effect of sex on the associations found, interaction analyses were performed. To assess the impact of ethnicity on the association between SES indicators and hypertension measures, we performed logistic regression analyses including interaction terms for each SES indicator*ethnicity. Comparisons were made between the model with and without the interaction term using an ANOVA-analysis. We tested for interaction only in cases where the association between a specific SES indicator and hypertension measure was statistically significant. Logistic regression outcomes were expressed in terms of odds ratios (OR) with corresponding 95% confidence intervals (CIs). Analyses with two-sides p-values of < 0.05 were considered statistically significant. Statistical analyses were performed using the computing environment R (Version 4.0.0, The R Foundation for Statistical Computing).

RESULTS

Characteristics of the population

Baseline characteristics of the study population stratified by ethnicity are shown in Table 2.1. Overall, 9,936 participants (54.9%) were female, among all six ethnicities this was evenly distributed. The median age of the cohort was 46 years [IQR 34, 54]. Turks and Moroccans tended to be younger compared to other ethnic groups. The mean BMI of the cohort was 26.86 (SD 5.07). Ghanaians and Turks had significant higher mean BMI (28.55 and 28.04) compared to the Dutch host populations (24.79). Diabetes mellitus was present in 1,550 participants (8.6%) and was most common in South-Asian Surinamese participants (16.4%). Overall, 5,963 participants had hypertension (32.9% of all participants). Individuals from Ghana had the highest prevalence of hypertension (53.4%), while Moroccans had the lowest prevalence (16.4%). Of all hypertensive participants, 56.5% was aware of their condition and 50.3% was treated. Greatest awareness (62.7%) was seen in African Surinamese, while the lowest (45.5%) was observed in participants of Turkish origin. Treatment rates were highest in the two Surinamese groups with 55.8% being treated, while the lowest treatment rate

Table 2.1: Baseline characteristics of study population stratified by ethnicity

Ethnicity	All	Dutch	South-Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
n	18,106	4,262	2,664	3,732	1,947	2,699	2,802
Sex (women %)	9,936 (54.9)	2,294 (53.8)	1,437 (53.9)	2,282 (61.1)	1,166 (59.9)	1,290 (47.8)	1,467 (52.4)
Age (median [IQR])	46.00 [34.00, 54.00]	48.00 [35.00, 58.00]	47.00 [36.00, 56.00]	51.00 [41.00, 57.00]	47.00 [39.00, 53.00]	41.00 [31.00, 49.00]	38.00 [29.00, 48.00]
Cardiovascular risk factors							
BMI (mean (SD))	26.86 (5.07)	24.79 (4.16)	26.33 (4.74)	27.88 (5.49)	28.50 (4.93)	28.04 (5.33)	26.87 (4.78)
Diabetes mellitus (%)	1,550 (8.6)	138 (3.3)	435 (16.4)	405 (10.9)	174 (9.0)	186 (6.9)	212 (7.6)
History of CVD (%)	932 (5.1)	157 (3.7)	238 (8.9)	196 (5.3)	85 (4.4)	175 (6.5)	81 (2.9)
Blood pressure							
Sys (mean (SD))	127.03 (17.76)	124.52 (16.38)	128.31 (18.20)	131.86 (18.25)	135.96 (19.01)	122.72 (15.54)	121.14 (15.42)
Dia (mean (SD))	79.20 (10.84)	77.33 (10.13)	80.09 (10.44)	82.06 (10.84)	84.64 (11.52)	77.76 (10.21)	75.00 (9.66)
Hypertension (%)	5,963 (32.9)	1,075 (25.2)	1,016 (38.1)	1,739 (46.6)	1,039 (53.4)	634 (23.5)	460 (16.4)
Awareness (%)	3,340 (56.5)	583 (54.4)	564 (56.1)	1082 (62.7)	611 (59.6)	286 (45.5)	214 (47.3)
Treatment (%)	2,997 (50.3)	474 (44.1)	567 (55.8)	971 (55.8)	546 (52.6)	274 (43.2)	165 (35.9)
Control (%)	1,383 (46.1)	265 (55.9)	256 (45.1)	418 (43.0)	200 (36.6)	155 (56.6)	89 (53.9)

Table 2.1: ***Continued***

Ethnicity	All	Dutch	South-Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
SES indicators							
Education (%)							
Higher	5,336 (29.5)	2,631 (61.7)	645 (24.2)	868 (23.3)	121 (6.2)	473 (17.5)	598 (21.3)
Intermediate	5,379 (29.7)	887 (20.8)	801 (30.1)	1,335 (35.8)	480 (24.7)	829 (30.7)	1,047 (37.4)
Lower	4,873 (26.9)	608 (14.3)	890 (33.4)	1,338 (35.9)	784 (40.3)	715 (26.5)	538 (19.2)
Never	2,518 (13.9)	136 (3.2)	328 (12.3)	191 (5.1)	562 (28.9)	682 (25.3)	619 (22.1)
Occupational status (%)							
Employed	12,336 (68.1)	3,278 (76.9)	1,780 (66.8)	2,455 (65.8)	1,282 (65.8)	1,769 (65.5)	1,772 (63.2)
Not in working population	2,082 (11.5)	629 (14.8)	274 (10.3)	382 (10.2)	84 (4.3)	335 (12.4)	378 (13.5)
Unemployed	2,314 (12.8)	234 (5.5)	361 (13.6)	556 (14.9)	411 (21.1)	351 (13.0)	401 (14.3)
Unfit for work	1,374 (7.6)	121 (2.8)	249 (9.3)	339 (9.1)	170 (8.7)	244 (9.0)	251 (9.0)
Occupational level (%)							
Higher	4,994 (27.6)	2,544 (59.7)	619 (23.2)	831 (22.3)	76 (3.9)	401 (14.9)	523 (18.7)
Middle	4,786 (26.4)	993 (23.3)	829 (31.1)	1,320 (35.4)	174 (8.9)	659 (24.4)	811 (28.9)
Lower	5,426 (30.0)	650 (15.3)	931 (34.9)	1,319 (35.3)	455 (23.4)	1,103 (40.9)	968 (34.5)
Elementary	2,900 (16.0)	75 (1.8)	285 (10.7)	262 (7.0)	1,242 (63.8)	536 (19.9)	500 (17.8)

BMI: body mass index; IQR: interquartile range; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; SES: socioeconomic status. Hypertension awareness and treatment are calculated among all hypertensives. Hypertension control is calculated among all hypertensives with medication usage.

was observed in Moroccans (35.9%). Of all participants with blood pressure lowering medication, 46.1% had controlled blood pressure rates. Controlled hypertension was the least prevalent among Ghanaians (36.6%) and African Surinamese (43.0%).

Most migrants had a low or intermediate educational level, while the proportion of individuals having a higher level of education was larger in individuals of Dutch origin. Overall, 68.1% of participants were employed, whereas only 7.6% was unfit for work. Greatest number of unemployment was seen in Ghanaians (21.1%), while the lowest (5.5%) was observed in the host population. The proportion of individuals working on a higher occupational level was larger in the Dutch population compared to the ethnic minority groups.

SES and hypertension prevalence

Lower education levels were associated with higher hypertension prevalence rates (Figure 2.2A). This effect remained significant after adjustment for ethnicity, BMI and diabetes (OR 1.45 [1.26-1.66]) for the lowest education level (Table 2.2A). Furthermore, regression analysis showed a significant association between hypertension prevalence and the other two SES indicators, when adjusting for age and sex (Figure 2.2A). In an age-sex adjusted model, being unemployed was associated with 1.39 [1.25-1.54] times higher odds for hypertension compared to being employed. A similar estimate was found after additionally adjusting for ethnicity (OR 1.30 [1.07-1.33]), but this association disappeared after additional adjustment for BMI, diabetes and history of cardiovascular disease (Table 2.2A). Compared to those with a higher occupational level, participants working in elementary occupations had an OR of 2.71 [2.44-3.02] for having hypertension (Figure 2.2A). This effect remained significant after adjustment for ethnicity, BMI and diabetes (OR 1.29 [1.12-1.48]).

SES and hypertension awareness

We found a significant association between hypertension awareness and occupational status, but not for educational or occupation level (Figure 2.2B). Participants unfit for work had a significant higher OR (1.24 [1.04-1.48]) for being aware of their hypertension, compared to those in the working population, however this association was not significant after adjustment for BMI, diabetes and history of cardiovascular disease (Table 2.2B).

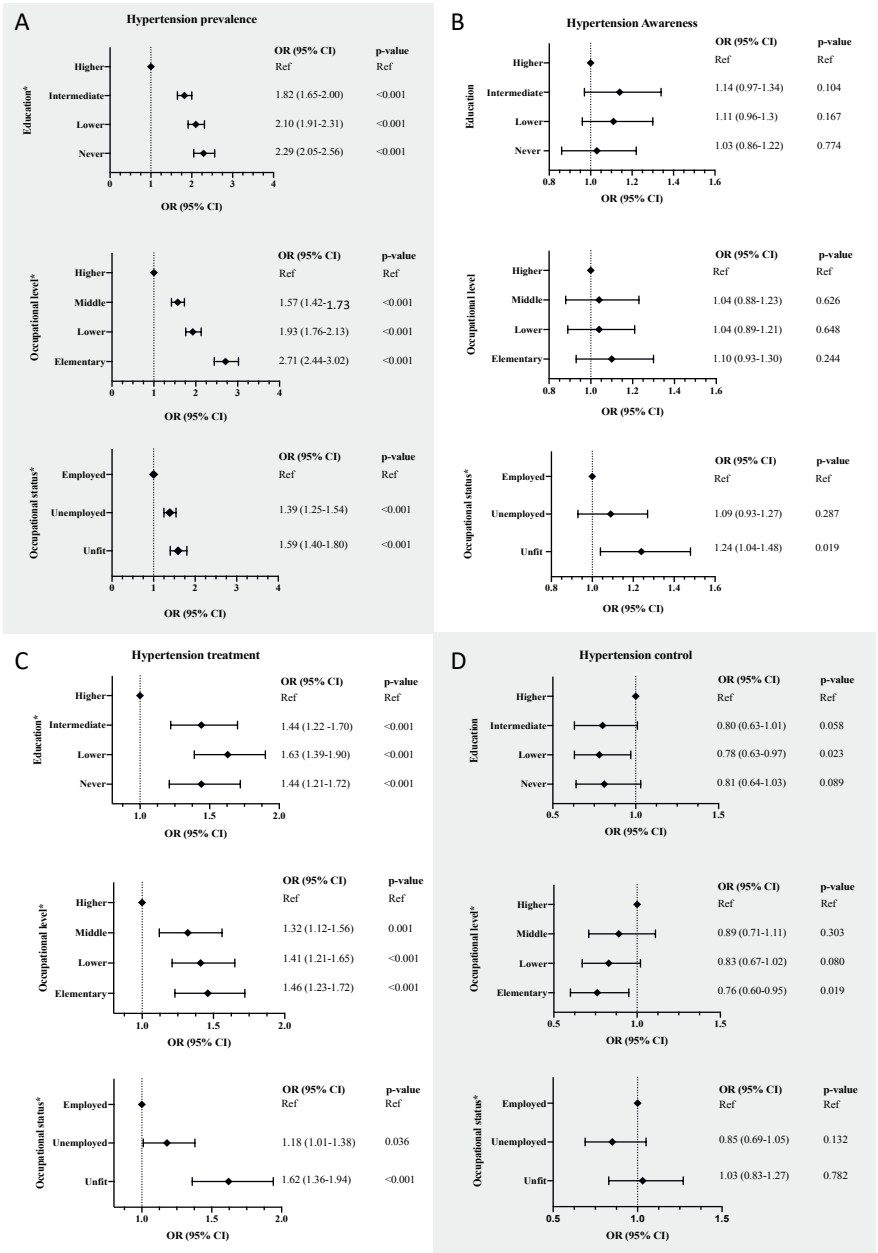

Figure 2.2: Hypertension prevalence, awareness, treatment and control and SES indicators education, occupational level and occupational status (adjusted for sex and age).
OR: odds ratio; CI: confidence interval; ref: reference; p-value of < 0.05 is significant; *: statistically significant for overall association. **A:** Hypertension prevalence, p-value is < 0.001 in all three logistic regression analyses. **B:** Hypertension awareness, p-value is only significant in the association between occupational status and awareness. **C:** Hypertension treatment, p-value is < 0.001 in all three regression analyses. **D:** Hypertension control, p-value is only significant (< 0.001) in the association between occupational status and control.

Table 2.2. Logistic regression analysis results for each adjustment model.
A. Hypertension prevalence and SES indicators (education, occupational status and occupational level).

	Model 2		Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education (n = 18,106)						
Higher	ref	ref	ref	ref	ref	ref
Intermediate	1.48 (1.33-1.66)	< 0.001	1.32 (1.18-1.47)	< 0.001	1.31 (1.17-1.46)	< 0.001
Lower	1.46 (1.31-1.63)	< 0.001	1.25 (1.12-1.39)	< 0.001	1.23 (1.10-1.37)	< 0.001
Never been to school/ Elementary	1.87 (1.63-2.15)	< 0.001	1.45 (1.26-1.66)	< 0.001	1.41 (1.22-1.61)	< 0.001
p-value for overall association: < 0.001						
Occupational status (n = 16,024)						
Employed	ref	ref	ref	ref	ref	ref
Unemployed	1.30 (1.07 - 1.33)	0.001	1.08 (0.97 - 1.21)	< 0.001	1.05 (0.94 - 1.17)	0.411
Unfit for work	1.42 (1.34 - 1.74)	< 0.001	1.26 (1.10 - 1.45)	0.001	1.15 (0.99 - 1.32)	0.062
p-value for overall association: < 0.001						
Occupational level (n = 18,106)						
Higher	ref	ref	ref	ref	ref	ref
Middle	1.30 (1.17-1.45)	< 0.001	1.16 (1.04-1.30)	0.008	1.15 (1.03-1.29)	0.014
Lower	1.53 (1.37-1.70)	< 0.001	1.31 (1.17-1.46)	< 0.001	1.28 (1.15-1.44)	< 0.001
Elementary	1.70 (1.48-1.94)	< 0.001	1.29 (1.12-1.48)	< 0.001	1.26 (1.10-1.46)	0.001
p-value for overall association: < 0.001						

Ref: reference group; OR: odds ratio; CI: confidence interval.
P-value for overall associations correspond to F-test for relation between SES and hypertension; after correcting for covariates. Model 2: adjusted for age, sex and ethnicity. Model 3: adjusted for age, sex, ethnicity, BMI and DM. Model 4: adjusted for age, sex, ethnicity, BMI, DM and history of CVD.

Table 2.2. *Continued*.
B. Hypertension awareness and SES indicators (education, occupational status and occupational level).

	Model 2		Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education (n = 5,963)						
Higher	ref	ref	ref	ref	ref	ref
Intermediate	1.06 (0.90-1.25)	0.489	1.04 (0.88-1.23)	0.683	1.02 (0.86-1.21)	0.818
Lower	1.01 (0.86-1.18)	0.919	0.97 (0.83-1.14)	0.744	0.96 (0.82-1.13)	0.626
Never been to school/ Elementary	0.96 (0.79-1.17)	0.692	0.90 (0.74-1.10)	0.299	0.88 (0.72-1.07)	0.197
p-value for overall association: 0.28						
Occupational status (n = 5,114)						
Employed	ref	ref	ref	ref	ref	ref
Unemployed	1.06 (0.91-1.24)	0.444	1.02 (0.88-1.20)	0.760	1.01 (0.86-1.18)	0.935
Unfit for work	1.28 (1.07-1.53)	0.008	1.19 (0.99-1.43)	0.067	1.12 (0.92-1.35)	0.258
p-value for overall association: < 0.001						
Occupational level (n = 5,963)						
Higher	ref	ref	ref	ref	ref	ref
Middle	0.99 (0.83-1.17)	0.863	0.96 (0.81-1.14)	0.665	0.96 (0.81-1.14)	0.665
Lower	0.96 (0.81-1.13)	0.608	0.92 (0.78-1.09)	0.335	0.92 (0.78-1.08)	0.304
Elementary	0.93 (0.76-1.14)	0.494	0.86 (0.70-1.06)	0.161	0.87 (0.70-1.06)	0.170
p-value for overall association: 0.63						

Ref: reference group; OR: odds ratio; CI: confidence interval.
P-value for overall associations correspond to F-test for relation between SES and hypertension; after correcting for covariates. Model 2: adjusted for age, sex and ethnicity. Model 3: adjusted for age, sex, ethnicity, BMI and DM. Model 4: adjusted for age, sex, ethnicity, BMI, DM and history of CVD.

Table 2.2. *Continued*.
C. Hypertension treatment and SES indicators (education, occupational status and occupational level).

	Model 2		Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education (n = 5,963)						
Higher	ref	ref	ref	ref	ref	ref
Intermediate	1.29 (1.09-1.53)	0.003	1.26 (1.06-1.50)	0.009	1.23 (1.03-1.47)	0.024
Lower	1.38 (1.17-1.63)	<0.001	1.32 (1.12-1.56)	0.001	1.26 (1.06-1.50)	0.008
Never been to school/ Elementary	1.24 (1.02-1.51)	0.030	1.14 (0.93-1.39)	0.199	1.07 (0.87-1.31)	0.528
p-value for overall association: <0.001						
Occupational status (n = 5,114)						
Employed	ref	ref	ref	ref	ref	ref
Unemployed	1.11 (0.95-1.30)	0.190	1.05 (0.90-1.24)	0.896	0.97 (0.82-1.15)	0.715
Unfit for work	1.57 (1.31-1.89)	<0.001	1.40 (1.16-1.70)	<0.001	1.21 (1.00-1.48)	0.055
p-value for overall association: <0.001						
Occupational level (n = 5,963)						
Higher	ref	ref	ref	ref	ref	ref
Middle	1.20 (1.01-1.42)	0.038	1.16 (0.97-1.38)	0.097	1.13 (0.95-1.36)	0.176
Lower	1.21 (1.03-1.43)	0.023	1.14 (0.96-1.35)	0.132	1.09 (0.91-1.30)	0.351
Elementary	1.13 (0.92-1.38)	0.250	1.00 (0.81-1.24)	0.978	0.97 (0.78-1.20)	0.758
p-value for overall association: <0.001						

Ref: reference group; OR: odds ratio; CI: confidence interval.
p-value for overall associations correspond to F-test for relation between SES and hypertension; after correcting for covariates. Model 2: adjusted for age, sex and ethnicity. Model 3: adjusted for age, sex, ethnicity, BMI and DM. Model 4: adjusted for age, sex, ethnicity, BMI, DM and history of CVD.

Table 2.2. *Continued*.
D. Hypertension control and SES indicators (education, occupational status and occupational level).

	Model 2		Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education (n = 2,997)						
Higher	ref	ref	ref	ref	ref	ref
Intermediate	0.89 (0.7-1.13)	0.341	0.89 (0.70-1.14)	0.362	0.89 (0.70-1.14)	0.366
Lower	0.91 (0.73-1.13)	0.379	0.95 (0.76-1.20)	0.682	0.92 (0.73-1.16)	0.490
Never been to school/ Elementary	0.85 (0.65-1.10)	0.222	0.93 (0.71-1.22)	0.613	0.91 (0.70-1.20)	0.517
p-value for overall association: 0.14						
Occupational status (n = 2,472)						
Employed	ref	ref	ref	ref	ref	ref
Unemployed	0.89 (0.72-1.11)	0.312	0.94 (0.75-1.17)	0.584	0.90 (0.72-1.13)	0.372
Unfit for work	0.98 (0.79-1.23)	0.891	1.04 (0.83-1.30)	0.715	0.99 (0.79-1.25)	0.949
p-value for overall association: <0.001						
Occupational level (n = 2,997)						
Higher	ref	ref	ref	ref	ref	ref
Middle	0.95 (0.76-1.20)	0.691	0.89 (0.71-1.11)	0.303	0.96 (0.78-1.18)	0.687
Lower	0.91 (0.73-1.14)	0.399	0.83 (0.67-1.02)	0.080	1.05 (0.81-1.36)	0.713
Elementary	0.97 (0.74-1.27)	0.803	0.76 (0.60-0.95)	0.019	0.99 (0.98-1,00)	0.115
p-value for overall association: 0.07						

Ref: reference group; OR: odds ratio; CI: confidence interval.
P-value for overall associations correspond to F-test for relation between SES and hypertension; after correcting for covariates.
Model 2: adjusted for age, sex and ethnicity. Model 3: adjusted for age, sex, ethnicity, BMI and DM. Model 4: adjusted for age, sex, ethnicity, BMI, DM and history of CVD.

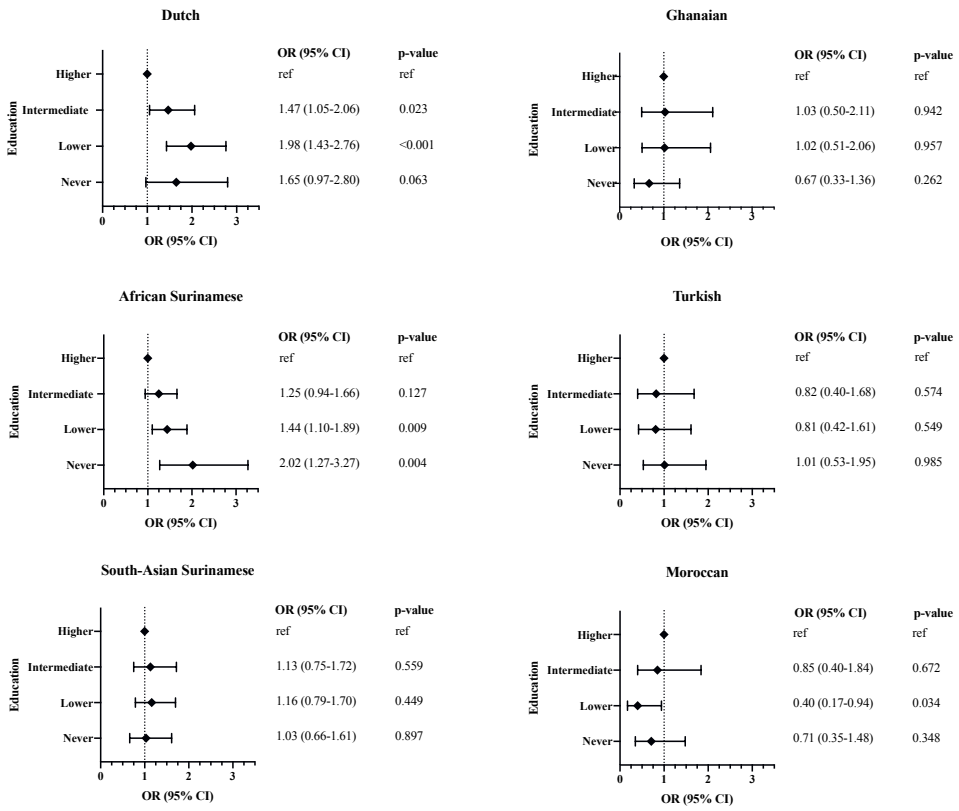

Figure 2.3: Ethnic specific odds ratios for the association between educational level and hypertension treatment, derived from the logistic regression model with interaction term (adjusted for age and sex).

OR: odds ratio; CI: confidence interval; p-value for trend < 0.05 is significant.

SES and hypertension treatment

In participants with hypertension, both educational level and occupational status were significantly associated with hypertension treatment levels (Figure 2.2C). Participants with lower educational level were 1.63 times [1.39-1.90] more likely to receive hypertension treatment, compared to those with a higher educational level in all four models (Table 2.2C). Participants without any or with elementary schooling only were more likely to be treated compared to those with the highest educational level (OR 1.44 [1.21-1.72], Figure 2.2C), also after adjustment for ethnicity, but this did not remain significant after additional adjustment for BMI, diabetes and history of cardiovascular disease (Table 2.2C). Being unemployed was significantly associated with a higher odds of hypertension treatment (OR 1.18 [1.01-1.38]) after adjustment for sex and

age (Figure 2.2C), but this association disappeared after additional adjustment for ethnicity (Table 2.2C).

In an age-sex adjusted model, the elementary occupational level was associated with 1.46 times [1.23-1.72] higher odds of receiving treatment, compared to the highest occupational level (Figure 2.2C). When additionally adjusting for ethnicity, BMI and diabetes with or without additional adjustment for cardiovascular disease, this association did not remain significant (Table 2.2C).

SES and hypertension control

Hypertension was less controlled among participants with elementary school or lower education (OR 0.78 [0.63-0.97] compared to those with higher level of education (Figure 2.2D). Participants with an elementary occupational level had lower rates of hypertension control (OR 0.76 [0.60-0.95]), compared to those with higher occupation level. These two associations did not remain significant after adjustment for ethnicity, BMI and diabetes (Table 2.2D). There was no association for hypertension control with other levels of education or occupational status (Figure 2.2D).

Impact of ethnicity on the associations between SES and hypertension

No significant interaction was found between sex and the SES indicators for all hypertension indicators. Therefore, we did not stratify by sex. Regarding hypertension prevalence, significant interaction was observed between ethnicity and the SES indicator education and occupational level ($p < 0.001$, see Supplemental Data File 2.3 and 2.4). In Dutch educated people, from the lowest (OR 3.16 [2.12-4.73]) to the intermediate level (OR 1.69 [1.39-2.06]), it was more likely that hypertension was present compared to those with a higher level of education from the same ethnic origin (Figure 2.3). This trend was also found in South-Asian Suriname and Turkish participants. In other ethnic minority groups this tendency was also apparent but was not significant ($p > 0.05$). Regarding occupational level, Turkish participants with elementary (OR 2.87 [1.97-4.24]) and lower (OR 2.09 [1.46-3.04]) level of occupation had higher odds of hypertension compared those with a higher occupational level from this ethnic origin. An equivalent tendency was seen for participants of Moroccan descent. In contrast, for Ghanaians and South-Asian Surinamese, there was no significant difference between the participants working on lower occupational level compared to those working on a higher level.

Impact of ethnicity on the relation between SES and hypertension awareness, treatment and control

No significant interactions were found between ethnicity and the SES indicators education, occupational status and occupational level ($p > 0.05$) and ethnicity did not significantly impact the association between hypertension awareness and SES. However, significant interaction between ethnicity and the SES indicator education was observed for hypertension treatment ($p < 0.05$, Figure 2.3). Dutch participants with lower (OR 1.98 [1.43-2.76]) and intermediate (OR 1.47 [1.05-2.06]) levels of education had higher odds of receiving treatment compared to Dutch with a higher level of education. In African Surinamese, those who never went to school or had elementary schooling were more likely (OR 2.02 [1.27-3.27]) to receive antihypertensive treatment compared to higher educated participants in this ethnic group, as were those with lower levels of education (OR 1.44 [1.10-1.89]). In contrast, Moroccans with lower level of education were less likely to receive antihypertensive therapy (OR 0.40 [0.17-0.94]), compared to those with a higher level of education in this group. There were no other differences between the ethnic groups in the associations between educational level, occupational status and occupational level and hypertension treatment ($p > 0.05$). Regarding hypertension control, no significant interaction between ethnicity and the SES indicators education, occupational status and occupational level were found ($p > 0.05$).

DISCUSSION

Key findings

In this large multi-ethnic population, lower SES was associated with higher hypertension prevalence, higher treatment levels and lower control rates.

Moreover, the association between hypertension prevalence and the SES indicators educational and occupational level differed between ethnic groups. Lower educated Dutch, South-Asian Surinamese and Turkish participants had higher odds for hypertension prevalence compared to higher educated individuals with the same ethnic background, while this was not observed for Ghanaians, African-Surinamese and Moroccans. Turkish and Moroccan participants had higher odds for hypertension prevalence when they were working on a lower occupational level compared to those working on a higher occupational level from the same ethnic origin. In contrast, this tendency was not found for Dutch, African-Surinamese, South-Asian Surinamese and

Ghanaians. Additionally, we found that participants unfit for work were more likely to be aware of hypertension than those in the working population.

Ethnic disparities were also observed in the association between hypertension treatment and the SES indicator education, with lower educated Dutch and African Surinamese participants having a higher odd of receiving antihypertensive treatment compared to those with a higher level of education, while the opposite was observed in Moroccan participants.

Discussion of key findings

The association of SES with hypertension prevalence found in this study in part confirms previous observations from both high- and middle-income countries and has been extensively documented in earlier research [6,11,17,18]. In all ethnic groups, lower SES was associated with higher hypertension prevalence rates, but there were no differences in hypertension awareness between individuals with lower and higher SES. This may point towards a relatively high accessibility of the Dutch health care system, which has a relatively low threshold resulting from universal health insurance coverage. This nationally mandatory health insurance is provided by private non-profit insurers and covers all health expenditures with free access to general practitioners' care and anti-hypertensive medication. Additionally, the Dutch healthcare system provides for reimbursement of healthcare expenditure for people with lower income, so that accessibility across all SES groups is maximally enhanced [19,20]. The effectiveness of these measures can be observed in previous research, which has demonstrated that in ethnic minority groups in the Netherlands, despite a lower SES as defined, among others, by income, healthcare utilization is not lower than in the Dutch origin population [21]. In fact, utilization of general practitioner services, primary responsible for hypertension treatment, was found to be higher across all migrant groups, possibly caused by more co-morbidity.

However, these associations may also result from a higher prevalence of comorbidities in individuals with lower SES, which may also explain why people who were unfit to work had a slightly higher chance of being aware, compared to employed individuals. This is consistent with previous findings from Howard et al., indicating that awareness is greater among individuals with a more adverse risk factor profile, and specifically among individuals with diabetes and a history of CVD [22].

In contrast to previous reports, in which lower education and occupational level were related to a lower probability of receiving anti-hypertensive treatment, we found an

inverse association between SES and hypertension treatment, where lower SES was associated with higher rates of hypertension treatment. Again, higher rates of adverse risk profiles in individuals with lower SES might lead to higher treatment rates, as we showed that ORs for hypertension treatment in different SES groups were substantially attenuated when adjusting for BMI and diabetes. In the Netherlands, the Dutch cardiovascular risk management guideline is used for decisions on drug treatment in hypertensive individuals. Deciding to start BP lowering medication not only depends on the level of SBP, DBP or the presence of diabetes, but also on the presence of other cardiovascular risk factors, such as smoking, family history of heart disease and high levels of cholesterol [23]. People from lower SES groups generally suffer from more cardiovascular risk factors and are therefore more likely to receive BP lowering medication [24,25]. In addition, although evidence on this topic is scare, it has been suggested that individuals with higher SES are more articulate in expressing preferences towards their physicians and might urge to postpone start of medication and await the effect of lifestyle changes [26]. Results from the SUNSET trial however contradict this, as no association was observed between education and hypertension treatment in Dutch, African-Surinamese and South-Asian Surinamese [27]. We hypothesize, that poor health outcomes among individuals with low SES has intensified the focus on low SES population by health care professionals, e.g. general practitioners, as reflected by the high treatment rate observed in our study.

Ethnicity played a significant role in the association between educational level and hypertension treatment. Dutch and Surinamese of both African and South-Asian descent with lower educational level were more likely to receive treatment compared to those with higher educational level, albeit not significant in South-Asians. The opposite was found for Moroccan individuals, who had lower hypertension treatment levels with lower educational, while the opposite was observed in Ghanaians and Turkish descent participants. As also African and South-Asian Surinamese speak Dutch as their native language, we estimate that these disparities may relate to the ability to speak Dutch, which reduces possible barriers in health care communication and access.

Finally, cultural and ethnic factors may play a role in the treatment and control rates of certain groups. We found that both people with lower education and the lowest occupational level were less likely to achieve blood pressure control compared to those with higher levels of education and occupational level. This is consistent with above mentioned research by Howard et al., showing that lower SES, defined by lower education and lower income, was related to less hypertension control in the USA.

In this study, they observed significant ethnic differences in hypertension control, that were only slightly reduced after adjustment for SES levels [22]. Findings from the multi-national EIGHT Study also show an increase of uncontrolled hypertension with a decreasing level of individual wealth, however, this was only observed in low-income and not middle-income countries. Additionally, Beune et al. have suggested that social, cultural or migration-related issues play a role in the association between lower SES and hypertension control [28]. Self-alteration of prescribed medication and cultural beliefs, including reliance on natural additives and perceived side-effects have been described as probable causes of low BP control in migrants [29]. Additionally, medication self-efficacy and social support have been identified as main determinants of adherence to medication recommendations among patients from African descents in the Netherlands [30]. Therefore, despite high healthcare consumption and treatment rate, limited medication adherence might lead to lower control in these groups. We hypothesize that comorbidity and health literacy and the penetration of prevention measures especially in migrants' communities are most relevant in the association between SES and hypertension awareness and treatment, but differences in ethnicity could be more valuable to focus on in hypertension control.

Although it is known that variables, such as BMI and DM, explain part of the differences in hypertension prevalence between ethnic groups, our aim was to include them in order to investigate their impact on the association between SES and hypertension across different ethnic groups. Based on these findings, we observed an important role for SES and ethnicity in hypertension management. We advocate for clinicians to consider the socioeconomic background of patients, of which most are generally well aware, in the management of hypertension by explaining therapy and giving lifestyle advice, especially in ethnic minority groups.

Strengths and limitations

The strengths of the HELIUS cohort are the inclusion of a large number of participants from several ethnic groups living in the same city and the collection of data from an extensive set of questionnaires and physical measurements. Outcomes and risk factors are measured based on the same methodology across all ethnic groups, including the majority population. The differences in baseline characteristics between ethnic groups are representative of the population living in the Netherlands.

Study limitations include first the lack of data on household income. It is possible that income may have differential effects on hypertension prevalence, awareness,

treatment and control. Notwithstanding cultural differences and reservations on the communication of household income, the Dutch health care system provides free health care to all with health insurance, and essentially all inhabitants, including migrants, are insured. Therefore we estimate that the role of financial status on hypertension awareness, treatment and control is limited [31]. Additionally, the indicators that we were able to include, such as education, have shown to be a powerful predictor for SES [32]. Second, although smoking causes an acute rise in blood pressure, the relation between chronic smoking and hypertension is less clear [33,34].

For the current analyses we excluded participants lacking one or more SES indicators. Compared to those with complete cases, excluded participants had a lower level of education and were more likely to be unemployed. We think however that by excluding people with lower SES, some associations might have been attenuated rather than overestimated.

For the analysis on occupational status, we excluded participants outside the working population, which may have caused overrepresentation of older participants in the excluded group. However, the dispersion of age in this group represented a considerable number of both younger students and older retirees that would otherwise interfere with our analysis on occupational status (see Supplemental Data File 2.2).

Finally, blood pressure measurements were based on an average of two measurements on a single visit, which might have overestimated the blood pressure levels due to the 'white-coat effect'. In a systematic review of previous studies, our group found no differences in white-coat effect between ethnic groups, therefore this is unlikely to have had substantial impact on the analyses 35. It is known that lower SES contributes to low health literacy and therefore could cause bias in reporting rates of self-reported use of BP lowering medication among individuals with lower SES.

Conclusion

Our study highlights that SES is associated with hypertension prevalence, treatment and control – but not awareness – in the Netherlands, and that the association between SES indicators and hypertension treatment differs between ethnic groups. We encourage clinicians to consider the socioeconomic background of patients, also in ethnic minority groups.

Acknowledgement

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REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics—2009 Update. *Circulation*; 119. Epub ahead of print 27 January 2009. DOI: 10.1161/CIRCULATIONAHA.108.191261.
2. Ashrafuzzaman M, Mazaharul Huq M, Chakraborty C, et al. Heart Attack Detection Using Smart Phone. *Int J Technol Enhanc Emerg Eng Res* 2013; 1: 23–27.
3. Hochstadt A, Chorin E, Viskin S, et al. Continuous heart rate monitoring for automatic detection of atrial fibrillation with novel bio-sensing technology. *J Electrocardiol* 2019; 52: 23–27.
4. Diederichsen SZ, Haugan KJ, Kronborg C, et al. Comprehensive Evaluation of Rhythm Monitoring Strategies in Screening for Atrial Fibrillation. *Circulation* 2020; 141: 1510–1522.
5. Selder J, Proesmans T, Breukel L, et al. Assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data. *Comput Methods Programs Biomed* 2020; 197: 105753.
6. Koenig N, Seeck A, Eckstein J, et al. Validation of a New Heart Rate Measurement Algorithm for Fingertip Recording of Video Signals with Smartphones. *Telemed e-Health* 2016; 22: 631–636.
7. Dur O, Rhoades C, Ng MS, et al. Design Rationale and Performance Evaluation of the Wavelet Health Wristband: Benchtop Validation of a Wrist-Worn Physiological Signal Recorder. *JMIR mHealth uHealth* 2018; 6: e11040.
8. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas* 2007; 28: R1–R39.
9. Perez M V., Mahaffey KW, Hedlin H, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; 381: 1909–1917.
10. Hochstadt A, Havakuk O, Chorin E, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. *J Electrocardiol* 2020; 60: 138–141.
11. Fallow BA, Tarumi T, Tanaka H. Influence of skin type and wavelength on light wave reflectance. *J Clin Monit Comput* 2013; 27: 313–317.

12. Boonya-ananta T, Rodriguez AJ, Ajmal A, et al. Synthetic photoplethysmography (PPG) of the radial artery through parallelized Monte Carlo and its correlation to body mass index (BMI). *Sci Rep* 2021; 11: 2570.
13. Sañudo B, De Hoyo M, Muñoz-López A, et al. Pilot Study Assessing the Influence of Skin Type on the Heart Rate Measurements Obtained by Photoplethysmography with the Apple Watch. *J Med Syst* 2019; 43: 195.
14. Hochstadt A, Havakuk O, Chorin E, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. *J Electrocardiol* 2020; 60: 138–141.
15. Li H, Huang S. A High-Efficiency and Real-Time Method for Quality Evaluation of PPG Signals. *IOP Conf Ser Mater Sci Eng* 2020; 711: 012100.
16. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988; 124: 869–871.
17. von Schuckmann LA, Hughes MC, Green AC, et al. Forearm hair density and risk of keratinocyte cancers in Australian adults. *Arch Dermatol Res* 2016; 308: 617–624.
18. Bordignon S, Corti MC, Bilato C. Atrial fibrillation associated with heart failure, stroke and mortality. *J Atr Fibrillation* 2012; 2: 53–61.
19. Kolk MZH, Blok S, De Wildt MCC, et al. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal*. Epub ahead of print 9 March 2021. DOI: 10.1093/ehjdh/ztab030.
20. Schäfer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability? *Int J Cardiol* 2013; 166: 15–29.
21. ANSI/AAMI. *Cardiac Monitors, Heart Rate Meters, and Alarms*. Arlington, 2002.

Supplemental Data File 2.1: Overview of characteristics of excluded participants on missing SES indicators

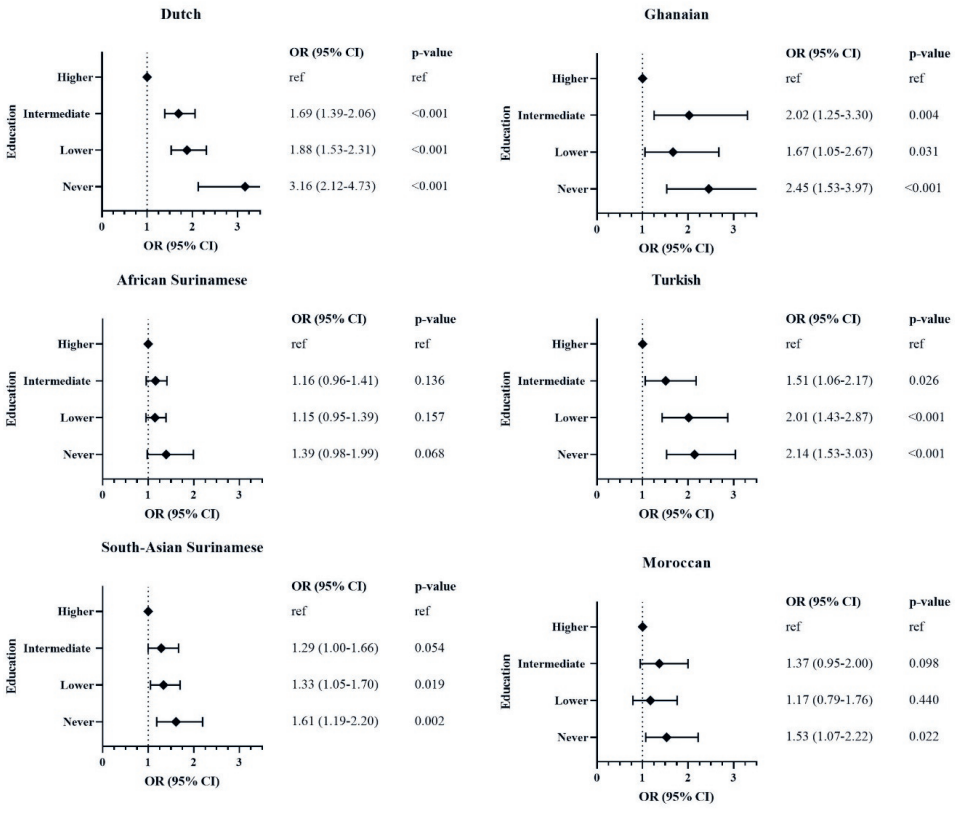
Missing SES indicators	None	Education	Occupational status	Occupational level
n	18,106	195	245	3,381
Ethnicity (%)				
Dutch	4,262 (23.5)	25 (12.8)	11 (4.5)	275 (8.1)
South-Asian Surinamese	2,664 (14.7)	16 (8.2)	33 (13.5)	364 (10.8)
Asian Surinamese	3,732 (20.6)	36 (18.5)	42 (17.1)	391 (11.6)
Ghanaian	1,947 (10.7)	42 (21.5)	53 (21.6)	372 (11.0)
Turkish	2,699 (14.9)	38 (19.5)	67 (27.3)	897 (26.5)
Moroccan	2,802 (15.4)	38 (19.5)	39 (15.9)	1,082 (32.0)
Sex (women (%))	9,936 (54.9)	112 (57.4)	152 (62.0)	2473 (73.1)
Age (median [IQR])	46.00 [34.00, 54.00]	49.00 [38.50, 56.50]	48.00 [39.00, 56.00]	45.00 [27.00, 54.00]
Blood pressure				
SBP (mean (SD))	127.03 (17.76)	128.50 (18.79)	131.13 (19.07)	126.19 (17.39)
DBP (mean (SD))	79.20 (10.84)	79.25 (10.94)	80.71 (11.43)	77.23 (10.19)
Hypertension (%)	5,963 (32.9)	76 (39.0)	107 (43.7)	1,044 (30.9)
SES indicators				
Education (%)				
Never	2,518 (13.9)		70 (36.5)	1,287 (39.4)
Lower	4,873 (26.9)		60 (31.2)	755 (23.1)
Intermediate	5,379 (29.7)		44 (22.9)	832 (25.5)
Higher	5,336 (29.5)		18 (9.4)	389 (11.9)
Occupational status (%)				
Employed	12,336 (68.1)	71 (50.0)		541 (17.2)
Not in working population	2,082 (11.5)	30 (21.1)		1,655 (52.8)
Unemployed	2,314 (12.8)	30 (21.1)		702 (22.4)
Unfit for work	1,374 (7.6)	11 (7.7)		239 (7.6)
Occupational level (%)				
Elementary	2,900 (16.0)	23 (29.9)		
Lower	5,426 (30.0)	26 (33.8)		
Middle	4,786 (26.4)	22 (28.6)		
Higher	4,994 (27.6)	6 (7.8)		

AS: African Surinamese; IQR: interquartile range; SAS; South-Asian Surinamese; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; SES: socioeconomic status. Total amount of excluded participants per missing SES indicator, n = 3,459, the table contains 'double' participants belonging to more than one column. If participants' data was missing on occupational status, they did not fill in occupational level as well.

Supplemental Data File 2.2: Overview of characteristics of participants stratified by occupational status

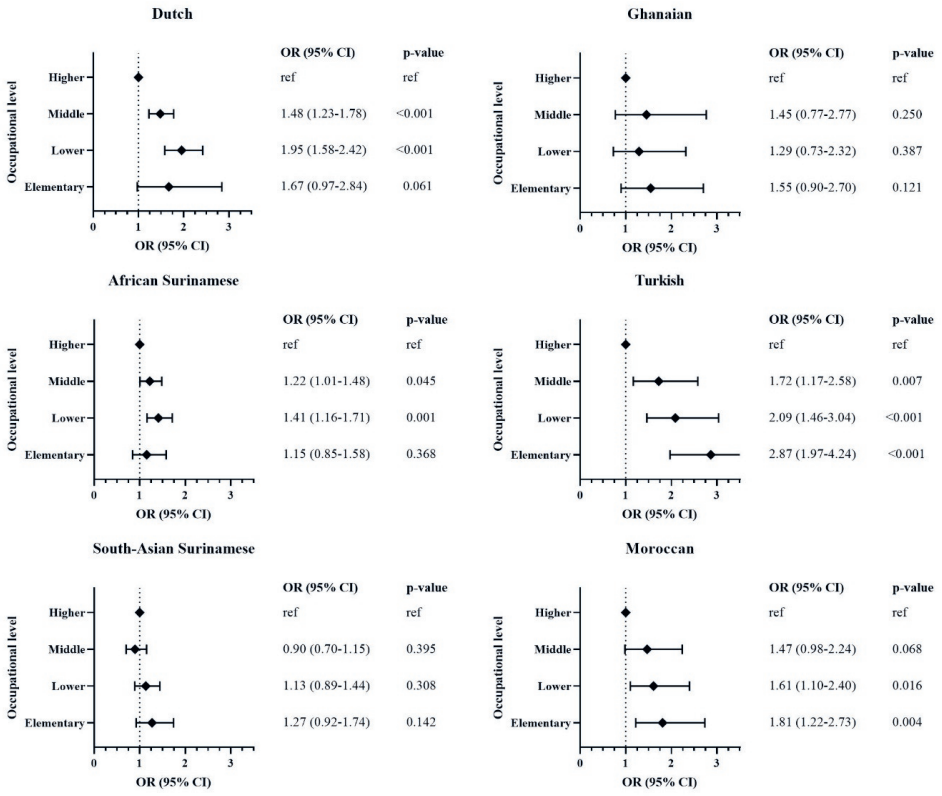
	Employed	Not in working population	Unemployed	Unfit for work
n	12,336	2,082	2,314	1,374
Women (%)	6,454 (52.3)	1,389 (66.7)	1,251 (54.1)	842 (61.3)
Age (median [IQR])	44.00 [33.00, 52.00]	59.00 [32.00, 66.00]	48.00 [38.00, 55.00]	53.00 [46.00, 59.00]
Ethnicity (%)				
Dutch	3,278 (26.6)	629 (30.2)	234 (10.1)	121 (8.8)
South-Asian Surinamese	1,780 (14.4)	274 (13.2)	361 (15.6)	249 (18.1)
African Surinamese	2,455 (19.9)	382 (18.3)	556 (24.0)	339 (24.7)
Ghanaian	1,282 (10.4)	84 (4.0)	411 (17.8)	170 (12.4)
Turkish	1,769 (14.3)	335 (16.1)	351 (15.2)	244 (17.8)
Moroccan	1,772 (14.4)	378 (18.2)	401 (17.3)	251 (18.3)
Cardiovascular risk factors				
SBP (mean (SD))	125.67 (16.86)	129.27 (20.01)	129.11 (18.34)	132.36 (19.24)
DBP (mean (SD))	78.93 (10.75)	77.36 (10.36)	81.07 (11.37)	81.22 (10.69)
Hypertension (%)	3,484 (28.2)	849 (40.8)	910 (39.3)	720 (52.4)
Diabetes mellitus (%)	716 (5.8)	270 (13.1)	267 (11.6)	297 (21.8)
BMI (median [IQR])	25.72 [23.06, 29.02]	26.45 [23.44, 30.03]	27.16 [24.02, 30.75]	28.37 [25.22, 32.31]
SES indicators				
Education (%)				
Never	1,235 (10.0)	389 (18.7)	489 (21.1)	405 (29.5)
Lower	2,938 (23.8)	638 (30.6)	816 (35.3)	481 (35.0)
Intermediate	3,800 (30.8)	609 (29.3)	650 (28.1)	320 (23.3)
Higher	4,363 (35.4)	446 (21.4)	359 (15.5)	168 (12.2)
Occupational level (%)				
Elementary	1,621 (13.1)	344 (16.5)	556 (24.0)	379 (27.6)
Lower	3,233 (26.2)	798 (38.3)	878 (37.9)	517 (37.6)
Middle	3,420 (27.7)	503 (24.2)	548 (23.7)	315 (22.9)
Higher	2,910 (23.6)	314 (15.1)	263 (11.4)	146 (10.6)
Scientific	1,152 (9.3)	123 (5.9)	69 (3.0)	17 (1.2)

IQR: interquartile range; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; SES: socioeconomic status. Total amount of participants is n = 18,106.

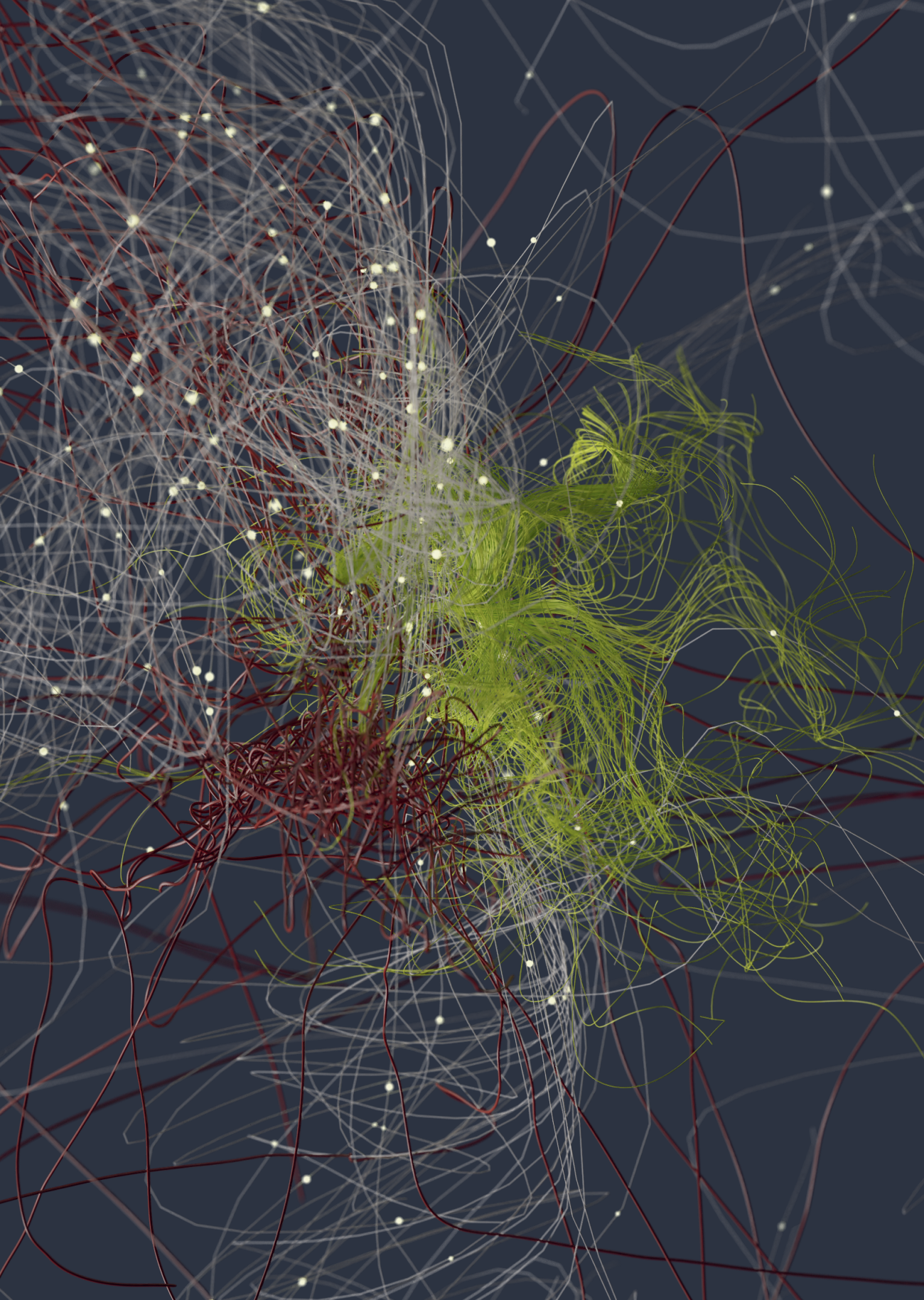


Supplemental Data File 2.3: Ethnic specific odds ratios for the association between education level and hypertension prevalence, derived from the logistic regression model with interaction term (adjusted for age and sex).

OR: odds ratio; CI: confidence interval; p-value < 0.05 is significant. P-value for trend is 0.001.



Supplemental Data File 2.4: Ethnic specific odds ratios for the association between occupational level and hypertension prevalence, derived from the logistic regression model with interaction term (adjusted for age and sex).
OR: odds ratio; CI: confidence interval; p-value < 0.05 is significant. P-value for trend is 0.001.



Chapter 3

Success factors in high-effect, low-cost eHealth programs for patients with hypertension – a systematic review and meta-analysis

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ABSTRACT

Background: eHealth programs can lower blood pressure but also drive healthcare costs. This study aims to review the evidence on effectiveness and costs of eHealth for hypertension and assess commonalities in programs with high effect and low additional cost.

Results: Overall, the incremental decrease of systolic blood pressure (SBP) using eHealth, compared to usual care, was 3.87 (95% CI 2.98-4.77) mmHg at six months and 5.68 (95% CI 4.77-6.59) mmHg at 12 months follow-up. High intensity interventions were more effective, resulting in a 2.6 (95% CI 0.5-4.7) (at 6 months) and 3.3 (95% CI 1.4-5.1) (at 12 months) lower SBP, but also more costly, resulting in €170 (95% CI 56-284) higher costs at 6 months and €342 (95% CI 128-556) at 12 months. Programs that included a high volume of participants showed €203 (95% CI 99-307) less costs than those with a low volume at 6 months, and €525 (95% CI 299-751) at 12 months without showing a difference in SBP. Studies that implemented eHealth as a partial replacement, rather than addition to usual care, were also less costly (€119 (95% CI -38-201 at 6 months and €346 (95% CI 261-430 at 12 months) without being less effective. Evidence on eHealth programs for hypertension is ambiguous, heterogeneity on effectiveness and costs is high (I^2 = 56-98%).

Conclusion: Effective eHealth with limited additional costs should focus on high intensity interventions, involve a large number of participants and use eHealth as a partial replacement of usual care.

INTRODUCTION

Hypertension is the strongest modifiable risk factor for cardiovascular disease and the leading cause of death worldwide. However, its global prevalence and associated cardiovascular complications have not been reduced, partly due to inadequacies in prevention, diagnosis and control [1]. Merely half of the adults with hypertension is aware of their condition, little over one in three were treated and as little as 14% had their blood pressure under control [2]. The emergence of new technologies could play an important role in improving these numbers [1,3]. Digital health and eHealth, and more specifically home- or telemonitoring, are the most promising emerging strategies, providing participants with the opportunity to remotely transfer physiological data such as blood pressure values [4]. However, adding technological innovation might drive healthcare costs upwards. Evidence on success factors for low-cost, high effect eHealth strategies for patients with hypertension is scarce and ambivalent [5,6].

In home blood pressure telemonitoring for hypertension, patients measure their blood pressure at home using medical devices. Ideally, values are remotely checked by a healthcare team, enabling swift therapeutic action. Evidence suggests that home monitoring of blood pressure through eHealth, if combined with additional support such as telecounseling or digital feedback, significantly lowers blood pressure in patients with hypertension compared to usual care [3].

However, eHealth strategies for home monitoring of blood pressure can be costly. Additional cost drivers in home blood pressure monitoring programs include hardware and software for each patient to allow them to perform measurements at home, the infrastructure to transfer results to a remote server and a dedicated team to monitor incoming data, and act upon them [7,8]. eHealth therefore requires new payment schemes that take additional (short-term) cost into account. On the other hand, prevention of cardiovascular events could significantly lower long-term costs. So far, the lack of adequate reimbursement schemes, leading to financially unsustainable eHealth programs, has prevented home monitoring from general and successful implementation into daily care [9]. This led to our primary research question: what are the differences in incremental effectiveness and costs of eHealth interventions for patients with hypertension, compared to usual care? Secondly, we investigated common characteristics in high effect, low cost eHealth programs.

METHODS

Data sources and search

This paper has been prepared in adherence to the PRISMA reporting guideline [10].

We searched the Pubmed, Cochrane and NIHR-HTA databases for studies in April 2020. The search was developed iteratively for synonyms of 'hypertension', 'home monitoring' and 'cost-effectiveness', using both controlled vocabulary (i.e. MeSH) and free text words (search strategy in supplementary materials). Paediatric studies, case reports, and reviews were excluded. We cross-checked the reference lists and the cited articles of the identified relevant papers for additional references.

Study selection

Studies were considered for inclusion if they fulfilled the following criteria: I. they described a randomised controlled trial; II. participants were diagnosed with hypertension; III. a home-monitoring or self-management infrastructure was compared with usual care, IV. the costs of the intervention were described and V. the minimal follow-up was at least 6 months. Studies should at least describe the difference in costs and systolic blood pressure between baseline and follow-up for both intervention and usual care. The home- or self-management infrastructure should be used for monitoring rather than diagnostic purposes and should be continuously used during the length of the study.

All identified studies were checked for eligibility for inclusion by two researchers (S.B. and E.L.) based on title and abstract. Hereafter, remaining potentially eligible studies were read in full and uncertainties were discussed by two authors (S.B. and E.L.). Disagreements concerning eligibility were resolved by discussion.

Data extraction and quality assessment

Data were extracted from the report of each trial on study design, publication year, number of included subjects, type of eHealth intervention, inclusion criteria of trial participants, costs and cost calculations and relevant endpoints as described above. If a study consisted of several comparisons between groups, e.g. different interventions, they were interpreted as separate studies.

To describe costs, we used the difference in total healthcare costs in Euro (€) during the study period. If costs were reported in other currencies than Euro, they were recalculated using the current currency rate as described by www.xe.com. We defined

effectiveness as the change in mean systolic blood pressure (SBP) in mmHg in the study period. The various interventions were compared on the incremental costs and SBP change separately.

For our statistical analysis we needed mean change on SBP and costs including standard deviation and number of participants for the intervention and control group. Missing data was handled as described in corresponding chapters of the Cochrane Handbook [11]. If instead of standard deviations only confidence intervals were available, standard deviations were calculated using the following formula:

$$SD = \sqrt{N} \times (upper\ limit - lower\ limit)/3.92$$

If no standard deviations for the change between baseline and follow-up were available, they were calculated, using the following formula:

$$SD_{change} = \sqrt{SD_{baseline}^2 + SD_{final}^2 - (2 \times Corr \times SD_{baseline} \times SD_{final}}$$

The correlation coefficient (Corr) was imputed from a comparable study, and was the average of the correlation coefficient in the experimental group and the control group, using the following formula:

$$Corr = \frac{SD_{baseline}^2 + SD_{final}^2 - SD_{change}^2}{2 \times SD_{baseline} \times SD_{final}}$$

If the standard error, but not the standard deviation was available, the standard deviation was calculated using the following formula:

$$SD = SE \times \sqrt{N}$$

If standard deviation of baseline, but not of follow-up data was available, the baseline standard deviation was also used for follow-up. If data on effect and costs were presented but SD, SE and confidence intervals were missing, the weighted average of the SD of other studies was used.

Based on literature on economics of eHealth we scored studies on three parameters: intensity of intervention, volume of participants and replacement of usual care. We then assessed whether studies that showed low additional costs and high additional effect had these parameters in common.

Intensity of intervention

While all eHealth systems are characterized by patient education, instructions and remote control, the extensiveness of those aspects differs from program to program. We classified all studies as intensive or non-intensive, based on a previously described intensity classification [3,12]. Intensive intervention was defined as self-monitoring with active intervention or self-monitoring with tailored support, for instance on education and feedback, and non-intensive as self-monitoring with no or automated instructions or feedback [12].

Volume of participants

While upfront investment costs to set up a digital eHealth infrastructure might be considerable, fixed and variable costs change very little per additional patient compared to usual care [13,14]. Therefore, an increasing number of participants of an eHealth program might decrease costs per patient (economy of scale). We calculated the average number of participants in the collected studies and compared the studies with a larger than average population with the smaller ones.

Replacing usual care

Through eHealth technologies, patients are enabled to remotely upload patient data to their care providers, thereby replacing or minimizing time-consuming and costly face-to-face consultations [14]. However, evidence on for instance adverse effects of replacing usual care with eHealth is limited [15]. Therefore, current programs either replace (parts of) usual care by for instance decreasing the amount of visits to general practitioner or outpatient clinic for patients participating in eHealth, or are used on top of it, which will influence total healthcare costs.

Risk of bias of individual studies was assessed using the Cochrane Collaboration Tool [16]. Risk of bias assessment included (i) sequence generation; (ii) allocation concealment; (iii) blinding of participants, personnel and investigators; (iv) incomplete data; (v) selective reporting of outcomes and (vi) other possible sources of bias.

Data synthesis and statistical analysis

We used the difference in mean reductions in systolic BP and healthcare costs between eHealth interventions and usual care. We performed a meta-analysis using fixed-effect methods in case of moderate or substantial heterogeneity, and random-effect methods in case of considerable heterogeneity. Heterogeneity was assessed using the I^2 test and

corresponding 95% confidence intervals (CIs) estimated using the formula proposed by Higgins and Thompson [17]. According to the Cochrane handbook, we interpreted levels of heterogeneity as follows [11]:

- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

A p-value less than 0.05 was set as the minimum level of statistical significance throughout the text.

RESULTS

The search in the three databases resulted in 289 potentially eligible studies (Figure 3.1). After screening on title and abstract and full text 15 studies were suitable for the quantitative analysis according to our predefined requirements, resulting in 15

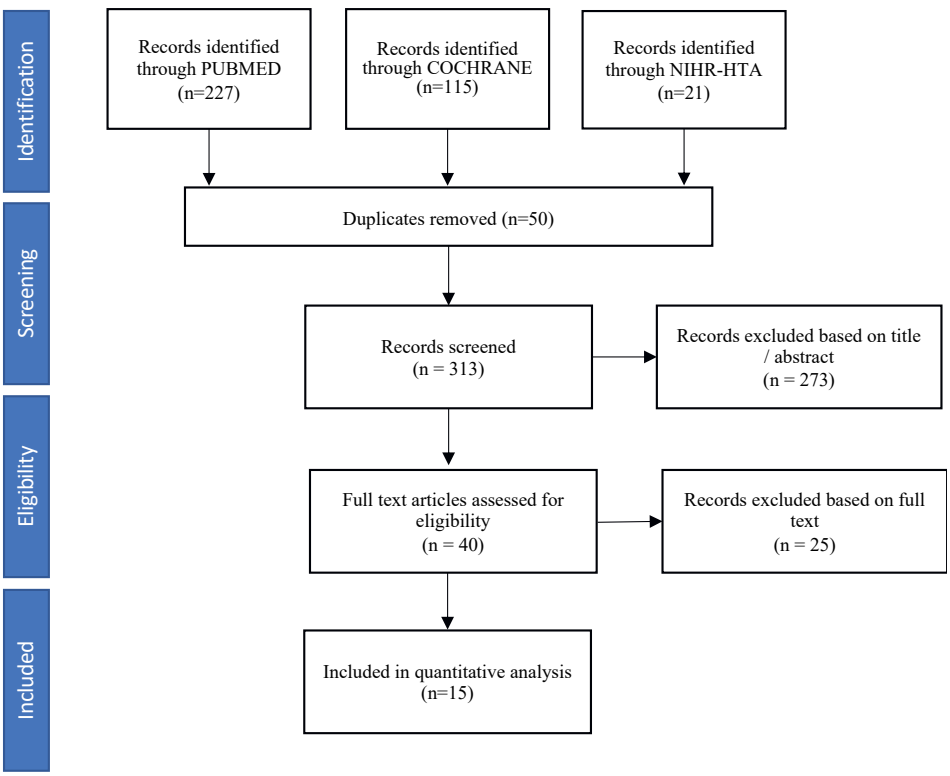

Figure 3.1: Literature search strategy based on PRISMA guidelines and selection of studies.

Table 3.1: BP, blood pressure; UC, usual care; HT, hypertension; CKD, chronic kidney disease; CV, cardiovascular. Characteristics of included studies

Article	Group size			Inclusion criteria					Design		
Author	Intervention group size	UC group size	Total group size	BP threshold	Age	# HT drugs	Specific co-morbidity	Baseline BP (intervention group)	Follow-up	eHealth replacing UC	Intervention intensity
[17] Soghikian (1992)	200	190	390	140/90	-	-	No	137/86	12 months	Yes	Low
[18] Friedman (1996	133	134	267	160/90	60+	≥ 1	No	170/86	6 months	No	Low
[19] McManus (2005)	224	227	451	140/85	35-75	≥ 1	No	158/89	6/12 months	Yes	Low
[20] Parati (2009)	187	111	298	140/90	18-75	-	No	149/89	6 months	Yes	Low
[21] Reed (2010)	183	62	245	-	-	≥ 1	No	126/72	12 months	No	High
[22] Madsen (2011)	115	118	233	150/95	20-80	-	No	153/91	6 months	Yes	High
[23] Bosworth (2011)	403	132	535	140/90	-	≥ 1	No	127/77	6/12 months	No	High
[24] Rifkin (2013)	22	15	37	140/90	50+	-	Stage 3 CKD	149/78	6 months	No	High
[25] Stoddart (2013)	200	201	401	145/85	18+	-	No	153/92	6 months	No	Low
[6] Kaambwa (2013)	234	246	480	140/90	35-85	≤ 2	No	152/85	6/12 months	Yes	High
[26] Fishman (2013)	520	258	778	140/90	25-75	≥ 1	No	152/89	12 months	No	Low/High
[27] Billups (2014)	162	164	326	140/90	18-79	≤ 3	No	149/90	6 months	Yes	High
[28] Penaloza-Ramos (2016)	220	230	450	130/80	> 35	≤ 3	CV History	144/80	12 months	Yes	High
[29] Dehmer (2018)	296	150	446	140/90	-	-	No	150/83	12 months	No	High
[30] Monahan (2019)	655	348	1,003	140/90 (> 145)	> 35	≤ 3	No	153/85	6/12 months	No	Low/High

comparisons between eHealth interventions and usual care at six months follow-up, and 15 at 12 months follow-up. The year of publication of the included studies varied from 1992 to 2019, they were performed in the United States (n = 8), UK (n = 5), Denmark (n = 1) and Italy (n = 1). In total, the studies included a total of 5,414 participants at six months follow-up and 5,593 at 12 months follow-up (Table 3.1).

Risk of bias

Figure 3.2 shows the summary of risk of bias for each individual study (n = 15). Blinding of participants and personnel (performance bias) is typically not possible in eHealth home monitoring studies, which is why for all included studies this item was labeled as high risk. Blinding of outcome assessment is possible but was not reported in over 50% of selected studies. Attribution rates are typically high in eHealth programs, in our selection of studies the rate varied between 6 and 25%. An overview of the assessment of risk of bias of each individual study is to be found in supplementary materials.

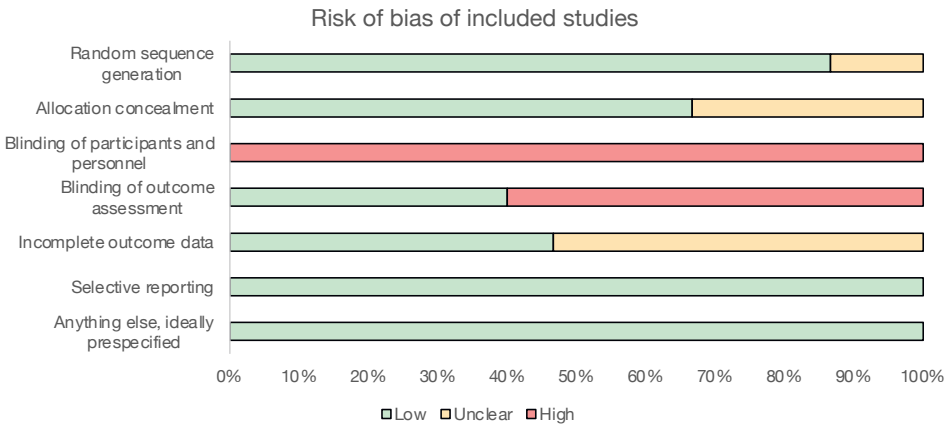

Figure 3.2: Risk of bias of included studies.

Overall effectiveness and costs

Overall, home monitoring of blood pressure was associated with a lower blood pressure at follow-up compared with usual care. The mean incremental decrease of SBP was 3.87 (95% CI 2.98-4.77) mmHg at six months follow-up, and 5.68 (95% CI 4.77-6.59) mmHg at 12 months follow-up (Figure 3.4). Heterogeneity on effectiveness between the studies was substantial at six months follow-up (I^2 = 71%), however was only moderate at 12 months (I^2 = 56%).

Healthcare costs per patient for the home monitoring programs were overall higher than costs for usual care. On average, costs within the study period were €119 (95% CI 74-166) higher at 6 months follow-up, and €238 (95% CI 174-303) at 12 months. However, heterogeneity on costs was considerable (I^2 = 98% at 6 months and 97% at twelve months).

Additional parameters

Overall, low intensity interventions showed less incremental effectivity and costs compared to high intensity, while providing the intervention to a large rather than a small volume of participants and using it as a (partial) replacement of care rather than as addition, decreased mean costs per patient without having an effect on blood pressure at follow-up (Figure 3.3).

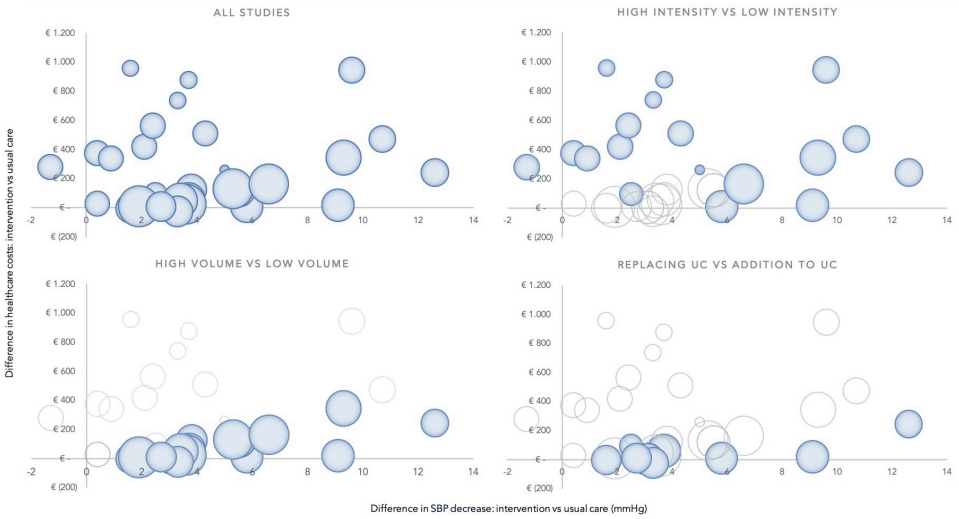

Figure 3.3: Incremental costs and effectiveness of the selected studies.
SBP, systolic blood pressure. The size of the surface of the balls reflects the study population in the intervention group.

Intensity of intervention

Seven studies reported on low intensity interventions [18–24], ten studies reported on high intensity interventions [7,23–31]. Studies with low intensity interventions showed a limited incremental decrease in SBP compared to usual care. At six months follow-up, low intensity programs achieved 2.43 (95% CI 1.1-3.8) mm Hg incremental SBP decrease, while studies with high intensity showed a 5.0 (95% CI 3.8-6.2) mm Hg decrease (Figure

3.4). At 12 months follow-up the difference remained and even enlarged slightly, with an incremental SBP decrease of 3.7 95% CI 2.2-5.1) mmHg for low intensity and 6.9 (95% CI 5.8-8.1) mmHg for high intensity Figure 3.4.

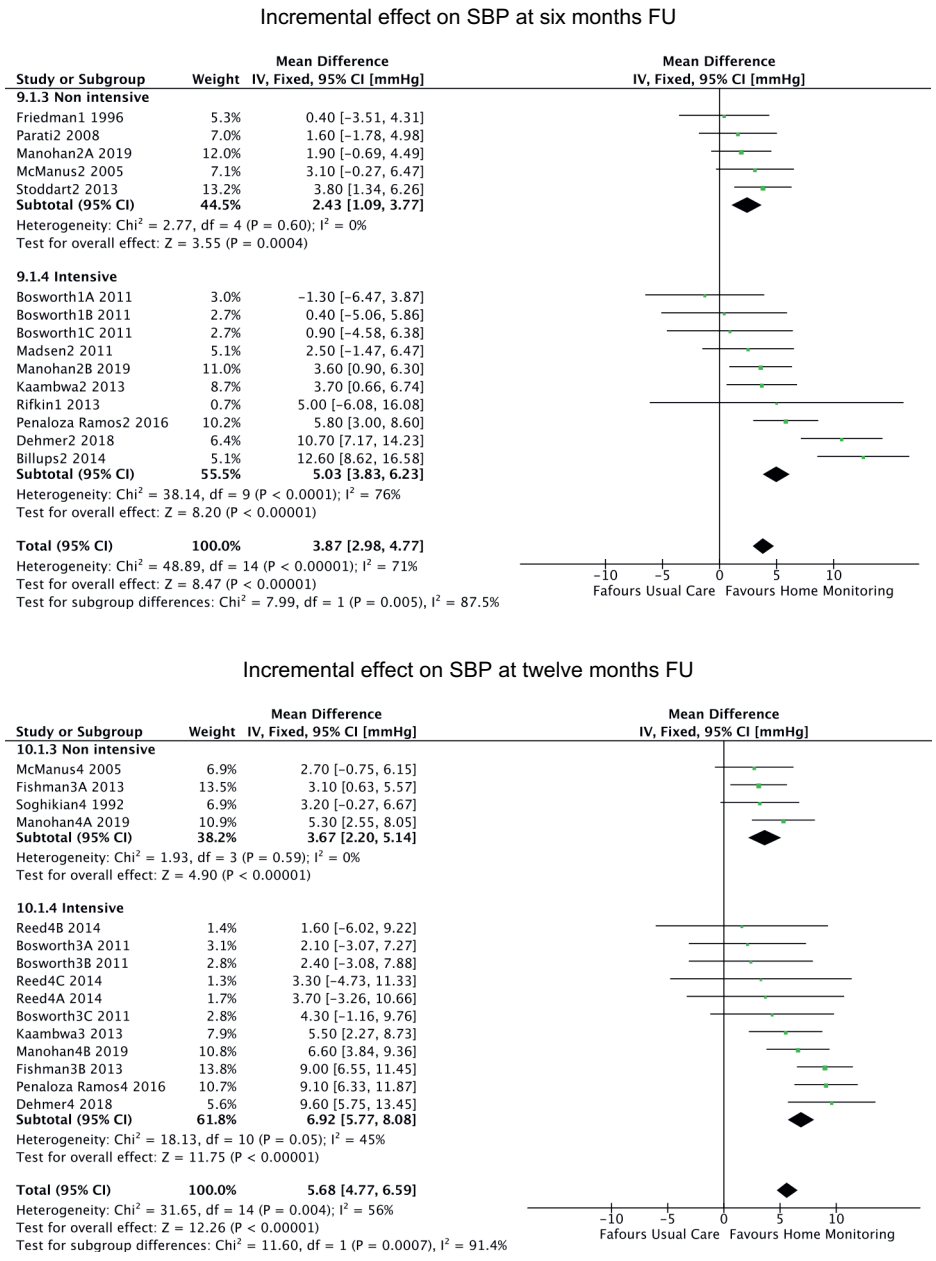

Figure 3.4: Incremental change in SBP at six and twelve months follow-up.
SBP, systolic blood pressure; FU, follow-up; CI, confidence interval.

Intensive home monitoring programs were more effective than non-intensive ones, but costs were also higher. Mean incremental costs per patient in the study period for the low intensity interventions were €34 (95% CI -38-105), compared to €203 (95% CI 114-293) in the high intensity group at six months follow-up. At 12 months the costs increased to €43 (95% CI -27-113) for low intensity and €385 (95% CI 183-587) for high intensity (Table 3.2).

Volume of participants

The average number of participants in the intervention group was 183, which was the cut-off point we used to divide the studies into low volume and high volume. Seven studies included less than average participants [19,21,25–29,31], eight included more [7,18,20,22–24,30]. There was no significant difference in incremental SBP decrease in the low-volume group compared to the high-volume group at both six and twelve months follow-up. However, the programs with a high volume of involved participants showed significantly lower costs per patient during the study period. At six months follow-up costs in the high volume group were €34 (95% CI 32-100), while in the low volume programs they accounted for €237 (95% CI 157-317). At twelve months the difference increased, as for high volume costs were €86 (95% CI 30-143), while for low volume they were €611 (95% CI 392-830) (Table 3.2).

Replacing usual care

For seven studies we were able to conclude that home monitoring was (partially) implemented to replace usual care [7,18,21,26,29,30,32], while in eight studies it was merely used as an addition [19,22,23,25,27,28,31]. There was no significant difference in incremental decrease of SBP in the studies that used eHealth as addition to and those that implemented it as a (partial) replacement of usual care. However, using eHealth as a partial replacement resulted into significant lower costs in the study period. At six months, costs in the replacement group were €53 (95% CI 3-103), in the addition group they accounted for €172 (95% CI 107-237). At twelve months, the costs in the replacement group were €11 less (95% CI -35-14) than usual care, while in the addition group they were €335 (95% CI 245-416) higher (Table 3.2).

Table 3.2: Incremental effectiveness and costs for three parameters

Outcome	Low intensity	95% CI	High intensity	95% CI	Difference	95% CI	Significance
SBP Change at 6 months (mmHg)	2.4	1.1 - 3.8	5.0	3.8 - 6.2	2.6	0.5 - 4.7	p = 0.005
SBP Change at 12 months (mmHg)	3.7	2.2 - 5.2	6.9	5.8 - 8.1	3.3	1.4 - 5.1	p = 0.0006
Incremental costs at 6 months (€)	34	-38 - 105	204	114 - 293	170	56 - 284	p = 0.004
Incremental costs at 12 months (€)	43	-27 - 113	385	183 - 587	342	128 - 556	p = 0.002
Outcome	Addition to UC	95% CI	Replacing UC	95% CI	Difference	95% CI	Significance
SBP Change at 6 months (mmHg)	3.3	2.1 - 4.5	4.7	3.3 - 6.0	1.4	-0.4 - 3.2	NS
SBP Change at 12 months (mmHg)	5.7	4.7 - 6.7	5.6	3.8 - 7.5	-0.1	-2.2 - 2.0	NS
Incremental costs at 6 months (€)	172	107 - 237	53	3 - 103	-119	-201 - 38	p = 0.004
Incremental costs at 12 months (€)	335	254 - 416	-11	-35 - 14	-346	-430 - -261	p < 0.00001
Outcome	Low volume	95% CI	High volume	95% CI	Difference	95% CI	Significance
SBP Change at 6 months (mmHg)	4.9	3.3 - 6.5	3.4	2.4 - 4.5	-1.4	-3.4 - 0.5	NS
SBP Change at 12 months (mmHg)	4.9	2.7 - 7.0	5.9	4.9 - 6.9	1.0	-1.3 - 3.3	NS
Incremental costs at 6 months (€)	237	157 - 317	34	-32 - 100	-203	-307 - -99	p = 0.0001
Incremental costs at 12 months (€)	611	392 - 830	86	30 - 143	-525	-751 - -299	p < 0.00001

CI, confidence interval; SBP, systolic blood pressure; UC, usual care.

DISCUSSION

Although evidence on effects and costs of eHealth programs for blood pressure management is heterogeneous, we found several parameters associated with considerable clinical effectiveness with limited additional cost. While a higher intensity of home monitoring leads to higher costs and a bigger effect on SBP, a high participant volume and using home monitoring as partial replacement of usual care lower the cost without affecting effectiveness. The combination of self-measurement of blood pressure, with active intervention or tailored remote support as a replacement of usual care in a large population tends to be the most successful on both parameters.

As previous research demonstrated, the most successful eHealth programs for the management of hypertension have shown to be cost-effective compared to usual care [24]. However, the critical factors leading to the relative success of these studies were unknown to date, which is why we aimed to identify them in this study. We used a previously described framework of intensity of intervention, which proved to be successful in predicting the effectiveness of home monitoring interventions. It is interesting to find that this framework has only limited value when costs and effectiveness are combined. Indeed, a low level of intensity is associated with low additional costs and low additional effect, while our results demonstrate that studies with a high level of intensity vary in both effectiveness and costs. The intensity level of the intervention is the first parameter we identified for home blood pressure monitoring that combine effectiveness with limited costs. As has been described elsewhere, a low level of intensity of the intervention is associated with limited effect [3,6]. Therefore, when designing an effective home monitoring scheme, it is mandatory to set up a high intensity level, an active remote intervention or tailored patient support. This will inevitably lead to a certain level of fixed costs, for instance for the set-up and availability of a dedicated remote healthcare team. Therefore, it is key to scale-up the monitoring program to a considerable number of participants to reduce cost per patient. The average study population of the papers included in our investigation was 183; we found that the ones with a larger amount of intervention participants showed lower additional costs per patient, without having an effect on systolic blood pressure at follow-up. The third parameter is to use the opportunities of home monitoring to save on events elsewhere in the care chain instead of just adding new activities, so that the additional costs of the programs can be partially abolished. We found several examples of this substitution of usual care by eHealth in the included studies, including the use of self-monitored instead of clinic BP readings to guide antihypertensive treatment decisions, train patients to self-titrate their antihypertensive medication following a predetermined plan and remotely check medication adherence [29,30,33]. We found that this replacement of visits to outpatient clinic or general practitioner by eHealth, while reducing costs, does not have less effect on systolic blood pressure at follow-up.

Generalizability of our results is limited, as the evidence on costs and effectiveness of home monitoring of blood pressure for patients with hypertension is not unambiguous. Studies selected in this paper varied with respect to how blood pressure was measured (e.g. office blood pressure measurement vs. ambulatory BP measurement), (additional) healthcare costs were calculated (e.g. only additional costs of intervention vs. total healthcare costs in study period vs. projected lifetime healthcare costs) and follow-up duration (6 months vs. 12 months). Studies were conducted in different countries,

although all high-income nations with developed healthcare systems, and discrepancies in healthcare- and reimbursement systems will have impacted costs presented in the studies. Similarly, studies were published over a long period (1992-2019) while covering the rapidly emerging field of eHealth, and although we did not find a correlation between study year and costs or effects this might have impacted the results. Lastly, factors outside the scope of this study, including treatment options and patient characteristics like educational level, socio economic status, age and other risk factors might impact the way in which low or high intensity eHealth interventions are perceived by the patient.

This lack of standardization in research methods and the absence of a useful framework to predict cost-effectiveness of home monitoring of hypertension mark the need for the identification of a set of standardized measures to better appreciate the associated costs of eHealth provision. Because of the ambiguity of the evidence in this field it remains difficult to assess whether home blood pressure monitoring using telemonitoring programs is cost-effective in general. Earlier attempts on meta-analyses reported similar issues on substantial heterogeneity of costs between the studies, underlining our finding that based on current evidence we cannot draw an overarching conclusion about cost-effectiveness of eHealth [5,6]. We did see, however, multiple successful examples that should lead the way in where we are heading with eHealth. Therefore, we can pursue the identification of common parameters among these studies that combine high incremental effectiveness with low incremental costs. Our paper provides these parameters, which can be used for designing new home monitoring programs, leading to scalable, affordable and effective eHealth. Such initiatives are especially necessary as suboptimal management of chronic diseases like hypertension increasingly count for accumulating socioeconomic costs.

Conclusion

eHealth programs for patients with hypertension, that are characterized by an intense remote intervention with high patient volumes and that (partly) replace usual care tend to demonstrate high effectiveness and limited costs. These success factors should be taken into account when designing new programs. Future research should focus on real-world experiences that represent economically viable and reimbursable programs, to further determine cost-effectiveness of eHealth for blood pressure management.

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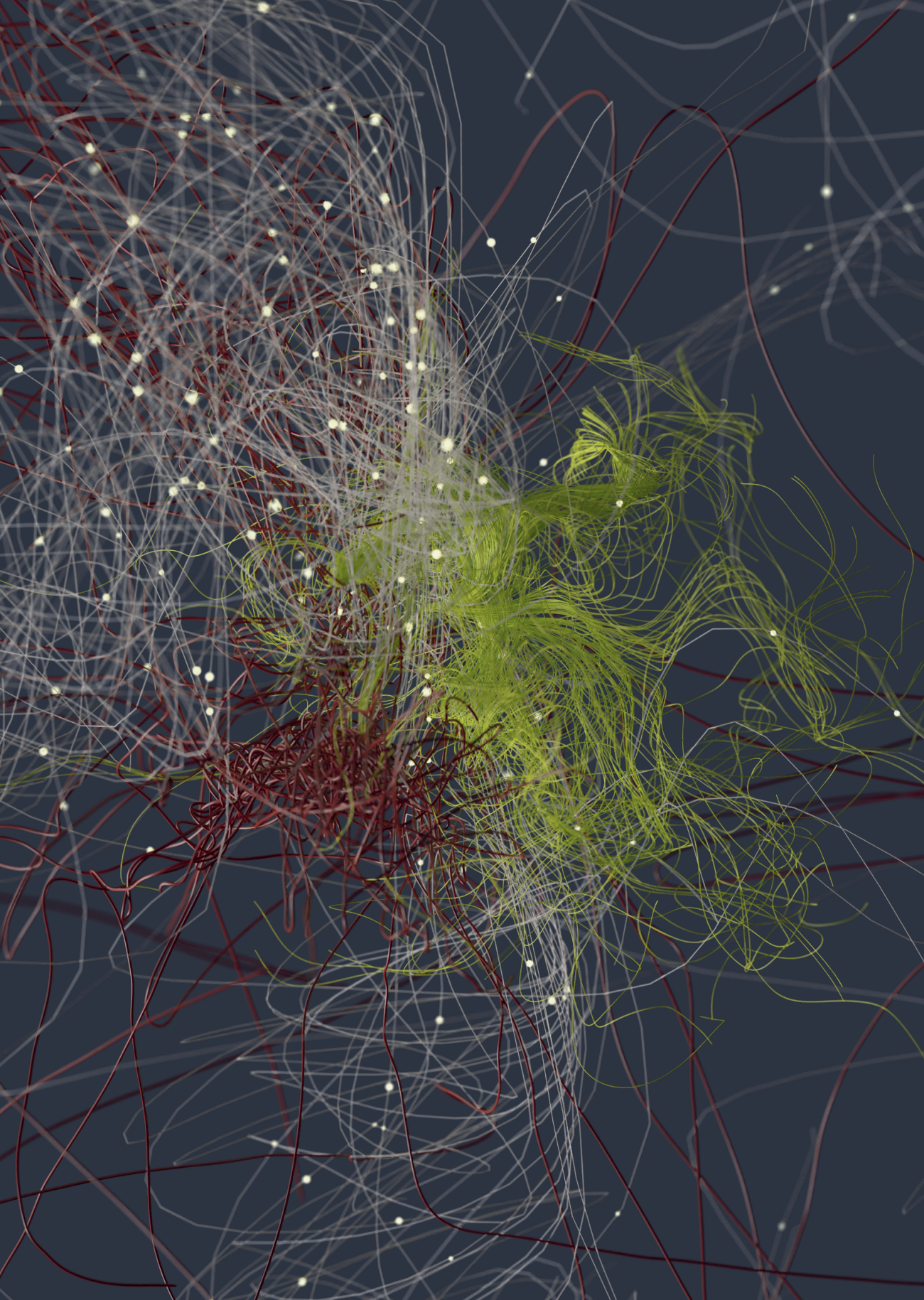
REFERENCES

1. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet* 2016; 388: 2665–2712.
2. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control. *Circulation* 2016; 134: 441–450.
3. Tucker KL, Earle K, Bray EP, et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. *PLOS Med* 2017; 14: e1002389.
4. Frederix I, Caiani EG, Dendale P, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019; 26: 1166–1177.
5. Omboni S, Gazzola T, Carabelli G, et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring. *J Hypertens* 2013; 31: 455–468.
6. Jacob V, Chattopadhyay SK, Proia KK, et al. Economics of Self-Measured Blood Pressure Monitoring: A Community Guide Systematic Review. *Am J Prev Med* 2017; 53: e105–e113.
7. Kaambwa B, Bryan S, Jowett S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a cost-effectiveness analysis. *Eur J Prev Cardiol* 2014; 21: 1517–1530.
8. Fukunaga H, Ohkubo T, Kobayashi M, et al. Cost-effectiveness of the introduction of home blood pressure measurement in patients with office hypertension. *J Hypertens* 2008; 26: 685–690.
9. Lindeman D, Young HM, Kidholm K, et al. Personalized Telehealth in the Future: A Global Research Agenda. *J Med Internet Res* 2016; 18: e53.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Reprinted from Annals of Internal Medicine). *Phys Ther* 2009; 89: 873–880.
11. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 6.0. Cochrane, 2019.
12. Uhlig K, Patel K, Ip S, et al. Self-Measured Blood Pressure Monitoring in the Management of Hypertension. *Ann Intern Med* 2013; 159: 185.
13. Schweitzer J, Synowiec C. The economics of eHealth and mHealth. *J Health Commun* 2012; 17: 73–81.
14. Elbert NJ, van Os-Medendorp H, van Renselaar W, et al. Effectiveness and Cost-Effectiveness of eHealth Interventions in Somatic Diseases: A Systematic Review of Systematic Reviews and Meta-Analyses. *J Med Internet Res* 2014; 16: e110.
15. Stevens WJM, van der Sande R, Beijer LJ, et al. eHealth Apps Replacing or Complementing Health Care Contacts: Scoping Review on Adverse Effects. *J Med Internet Res* 2019; 21: e10736.
16. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: 1–9.
17. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
18. Soghikian K, Casper SM, Fireman BH, et al. Home blood pressure monitoring. Effect on use of medical services and medical care costs. *Med Care* 1992; 30: 855–865.

19. Friedman RH, Kazis LE, Jette A, et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *Am J Hypertens* 1996; 9: 285–292.
20. McManus RJ, Mant J, Roalfe A, et al. Targets and self monitoring in hypertension: Randomised controlled trial and cost effectiveness analysis. *Br Med J* 2005; 331: 493–496.
21. Parati G, Omboni S, Albini F, et al. Home blood pressure telemonitoring improves hypertension control in general practice. The TeleBPCare study. *J Hypertens* 2009; 27: 198–203.
22. Stoddart A, Hanley J, Wild S, et al. Telemonitoring-based service redesign for the management of uncontrolled hypertension (HITS): cost and cost-effectiveness analysis of a randomised controlled trial. *BMJ Open*; 3. Epub ahead of print May 2013. DOI: 10.1136/bmjopen-2013-002681.
23. Fishman PA, Cook AJ, Anderson ML, et al. Improving BP control through electronic communications: an economic evaluation. *Am J Manag Care* 2013; 19: 709–716.
24. Monahan M, Jowett S, Nickless A, et al. Cost-Effectiveness of Telemonitoring and Self-Monitoring of Blood Pressure for Antihypertensive Titration in Primary Care (TASMINH4). *Hypertension* 2019; 73: 1231–1239.
25. Reed SD, Li Y, Oddone EZ, et al. Economic evaluation of home blood pressure monitoring with or without telephonic behavioral self-management in patients with hypertension. *Am J Hypertens* 2010; 23: 142–148.
26. Madsen LB, Christiansen T, Kirkegaard P, et al. Economic evaluation of home blood pressure telemonitoring: a randomized controlled trial. *Blood Press* 2011; 20: 117–125.
27. Bosworth HB, Powers BJ, Olsen MK, et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. *Arch Intern Med* 2011; 171: 1173–1180.
28. Rifkin DE, Abdelmalek JA, Miracle CM, et al. Linking clinic and home: a randomized, controlled clinical effectiveness trial of real-time, wireless blood pressure monitoring for older patients with kidney disease and hypertension. *Blood Press Monit* 2013; 18: 8–15.
29. Billups SJ, Moore LR, Olson KL, et al. Cost-effectiveness evaluation of a home blood pressure monitoring program. *Am J Manag Care* 2014; 20: e380–7.
30. Penaloza-Ramos MC, Jowett S, Mant J, et al. Cost-effectiveness of self-management of blood pressure in hypertensive patients over 70 years with suboptimal control and established cardiovascular disease or additional cardiovascular risk diseases (TASMIN-SR). *Eur J Prev Cardiol* 2016; 23: 902–912.
31. Dehmer SP, Maciosek MV, Trower NK, et al. Economic evaluation of the home blood pressure telemonitoring and pharmacist case management to control hypertension (Hyperlink) trial. *JACCP J Am Coll Clin Pharm* 2018; 1: 21–30.
32. McManus RJ, Mant J, Roalfe A, et al. A randomised controlled trial of patient held targets and self monitoring in the control of hypertension. *Am J Hypertens* 2005; 18: A90, Abstract no: P233.
33. Monahan M, Jowett S, Lovibond K, et al. Predicting Out-of-Office Blood Pressure in the Clinic for the Diagnosis of Hypertension in Primary Care: An Economic Evaluation. *Hypertens (Dallas, Tex 1979)* 2018; 71: 250–261.



Chapter 4

Protecting patient privacy in digital health technology: the Dutch mHealth infrastructure of HartWacht as a learning case

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ABSTRACT

Innovative ways of healthcare delivery like mHealth, the practice of medicine by mobile devices and wearable devices, is a promising new technique that may lead to improvement in quality of care at lower costs. While fully acknowledging the importance of mHealth development, there are challenges on privacy legislation. We address the legal framework, especially the General Data Protection Regulation (GDPR), applied to mHealth and its implications for mHealth developments in Europe. We discuss how these rules are applied using a representative example of a mHealth program with remote monitoring in the Netherlands. We consider informing patients about the data processing and obtaining their explicit consent as main responsibilities of healthcare providers introducing mHealth in their practice.

INTRODUCTION

Healthcare systems worldwide are facing new challenges such as an aging population, inadequate delivery of medical resources and increasing budgetary pressure [1]. Innovative ways of healthcare delivery, such as mobile health (mHealth), are rapidly gaining ground in the pursuit to face these challenges. mHealth is a subtheme of eHealth (the use of ICT in health) [2,3] and is defined as the practice of medicine by mobile devices (i.e. mobile phones and tablets) and wearable devices (i.e. smart watches, mobile single lead electrocardiograms) [4,5]. Monitoring patients outside a hospital with mHealth is likely to increase patient's health status at decreased expenditure [6]. Although mHealth is promising, it poses important challenges on privacy, data protection and data security [7].

In 2016, the parliament of the European Union (EU) adopted the General Data Protection Regulation (GDPR), which came into force in May 2018 [8,9]. Already in 2012, the European Commission of the EU proposed a comprehensive reform of the earlier EU's privacy directive (Directive 95/46/EC, dating back to 1995). In light of the rapid digitalization, a strong and more coherent data protection framework was considered necessary to protect individuals with regard to the processing and free movement of their personal data. Since mHealth depends heavily on the collection, storage, transfer, and interpretation of patients' personal (health) data, each mHealth infrastructure, set up within the EU's territorial scope (Article 3 GDPR), should be in accordance with the GDPR's provisions [5]. The scope of the Regulation includes all data processing carried out by a medical center or company based in the EU. Ensuring GDPR-compliance is not only important to safeguard legitimate data processing, but also to keep the confidence of patients who entrust their data and privacy to their doctors. Institutions that use personal data and fail to comply can face penalties that can be up to 4% of previous year's turnover [10].

In a responsible mHealth infrastructure, all data processing should meet the requirements of the GDPR. To facilitate further mHealth development in the EU, we provide a comprehensible step-by-step roadmap on how to set-up a GDPR-proof mHealth infrastructure. As an example, we provide our own mHealth infrastructure that was recently introduced in the Netherlands (HartWacht). We examine the challenges we encountered with regards to HartWacht and the GDPR. Finally, we discuss possible pitfalls healthcare providers should be aware of when introducing a GDPR-compliant mHealth infrastructure.

HartWacht: a Dutch example of a mHealth infrastructure

In 2016, *Hartwacht* – a system to monitor patients with widespread heart diseases – was introduced in the Netherlands. It enables patients to perform health measurements at home. The program is set up for three patient groups: patients with cardiac arrhythmias, patients with hypertension and patients with congestive heart failure. Cardiology Centers of the Netherlands (CCN) serves as healthcare provider (HCP). Devices (hardware) and applications (software) are provided by several partners. The devices are connected to the applications for smartphone, tablet or personal computer. Collected health data are transferred to CCN, through partner servers, and integrated in the electronic patient files. Incoming health data are interpreted by dedicated nurses under the supervision of a cardiologist. If necessary, this team contacts the patient or the treating physician (see Figure 4.1).

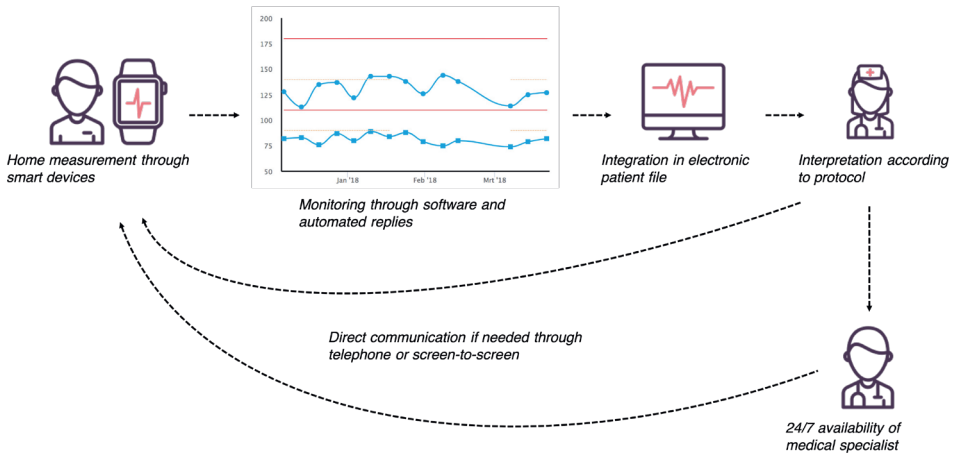


Figure 4.1: The HartWacht program.

Data processing within HartWacht

For proper functioning of the Dutch heart disease surveillance system, large amounts of personal health data need to be collected, stored, transferred, shared and interpreted. Figure 4.2 shows an overview of data processing within HartWacht. For each of these phases different articles from the GDPR are applicable. We will describe every phase with its corresponding relevant GDPR articles and show the experience of HartWacht in complying with GDPR. An overview is presented in Table 4.1.

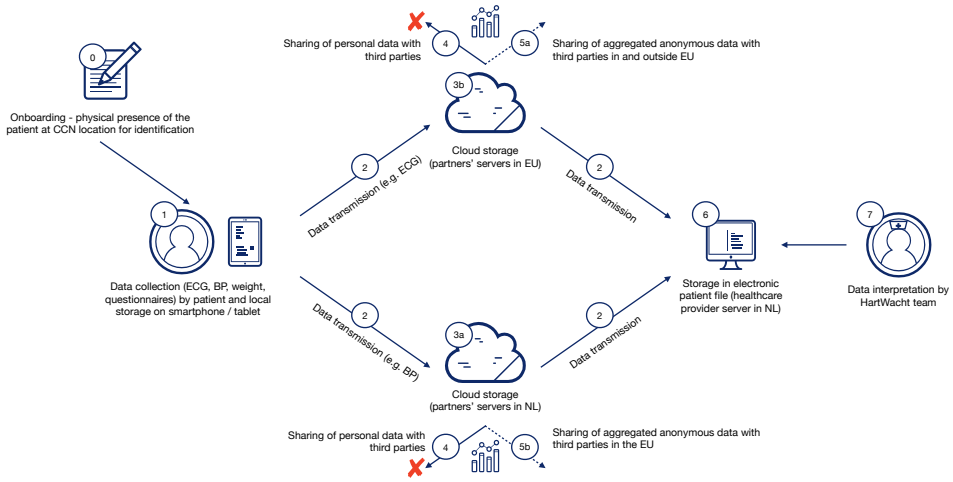


Figure 4.2: Data flow of the HartWacht infrastructure.

Implications of GDPR for mHealth infrastructures

Compliance with GDPR

In May 2018 the GDPR came into force with as its main goal to offer protecting to all EU-citizens with respect to the processing of their personal data [8]. The GDPR has consequences for the emerging field of mHealth, which is almost completely dependent on the processing of health data. It is the responsibility of each HCP initiating a mHealth program '(…) to ensure and to be able to demonstrate that processing is performed in accordance with (…) [the GDPR]', this by implementing appropriate technical and organizational measures to secure the data processing (Article 24 paragraph 1 GDPR).

Health data are identified in the GDPR as a 'special category'. This means they are protected by a stricter privacy regime than other, 'regular', data [11,12]. Health data are broadly defined as "data related to the physical or mental health of a natural person" (Article 4 GDPR), and this clearly includes data on someone's physical condition collected with mobile and/or wearable devices [8]. As misuse of health data can have severe and extensive consequences for individuals, the processing of such data is prohibited, with only few exceptions (Article 9 GDPR).

In light of the GDPR, three 'stakeholders' are relevant in an mHealth home monitoring infrastructure. First, the data subject (hereafter 'the patient'): a person that can be identified through the data that are used in mHealth and whose rights are protected in the regulation (Article 4 paragraph 1 GDPR). Second, the data controller (hereafter

'the healthcare provider' or HCP): the institution, and on its behalf, the responsible healthcare provider(s), that determine the purposes and means of the data processing (Article 4 paragraph 7 GDPR). Third, the data processor (hereafter 'the company'): the private party or parties that deliver the mHealth infrastructure and process data in this respect (Article 4 paragraph 8 GDPR).

Company that provides mHealth infrastructure

Before offering mHealth to patients, the HCP – as data controller – makes a clear agreement with his processor, the company that provides the appropriate infrastructure. In their agreement – called a 'data processing agreement' (DPA) – they decide on the specific purpose and nature of the data processing (Article 28 paragraph 3 GDPR). Because the processor acts on behalf of the controller, the HCP is the party that determines the content and conditions of the agreement, and the company the party that assists the controller with compliance with the obligations of the GDPR. Would a company, established outside the EU, be involved in mHealth, offered to patients in the EU, it would still be bound by the provisions of the GDPR (Article 3 paragraph 1 GDPR).

0. Onboarding of patient

In order to ensure correct identification, the patient is physically present on site when the mHealth program is started. The patient provides consent – in this case: for a health monitoring program – to his HCP. Consent needs to be obtained before any data collecting or processing; it should be freely given, and be based on sufficient and clear information, including the identity of all parties receiving patient data. In the Netherlands, the doctor-patient is regulated by civil law – by the 'Medical Treatment Contract Act' – although it can also be regulated by public law. An important provision of this act is the one that ensures medical confidentiality, implying that patient data may not be shared with professionals that are not involved in the patient's treatment without prior consent.

Apart from the Medical Treatment Contract Act, the GDPR requires informed consent (Article 7 GDPR), but in this case specifically for processing the patient's data. It is again the HCP who is responsible for informing the patient and asks his or her consent *before* any data collection or processing is carried out; consent should be freely given, and be based on sufficient and clear information, including the identity of the HCP as controller and all parties receiving patient data (Article 13 GDPR). Written consent is not required, however, as long as '*the controller [HCP] shall be able to demonstrate*

that the data subject has consented' (Article 7 paragraph 1 GDPR). The patient has the option to withdraw consent, after which the mHealth program and data collection should be terminated.

1. Health data collection

Health data are collected by patients through medical devices that are connected with an application on smartphone or tablet after preferably a safe login with two-factor authentication. After performing measurements, data are (partly) stored locally on the smart devices owned by the patients.

2. Health data transmission

Health data that are recorded by the patient are transferred to servers of the company that is engaged in mHealth as data processor. It is the HPC's responsibility to cooperate only with data processors *providing sufficient guarantees to implement appropriate technical and organisational measures in such a manner that processing will meet the requirements of the GDPR and ensure the protection of the rights of the data subject* (Article 28 paragraph 1 GDPR). In order to minimize risks of incidents during the transmission of the data, both parties – the HCP and the company – are responsible to implement appropriate technical and organizational measures to secure data transmission. In general, because health data are considered highly sensitive, those measures should provide the highest level of protection. Although data encryption is explicitly mentioned as an appropriate measure (Article 32 paragraph 1 GDPR), the GDPR doesn't describe which encryption methods are considered adequate. In general, however, in case of processing health data, encryption methods as described in IT-security guidelines or standards, such as ISO/ICE 27001 are required (Article 43 paragraph 1 sub b GDPR). However useful it may be to involve cloud services for data transmission (because of their increased scalability and flexibility), it obviously implies enlarged risk of infringing security and patient confidentiality. It is important that the HCP knows if the company involves cloud services (including their geographical location) in providing its services and is notified when personal data breaches occur (Article 33 GDPR).

3. Health data storage on external servers

After transfer, health data are stored on servers of the company. In its role as controller, the HCP needs to imply appropriate technical and organizational measures to ensure that only the data that are necessary for the specific purpose of the cooperation are collected and stored (data minimization) (Article 25 paragraph 2 GDPR).

Table 4.1: Phases of data processing and implications from data protection legislation (GDPR)

Phase	Element	Implications from data protection legislation (GDPR)	Points of attention	HartWacht learning points
0	Onboarding of patient	• The patient is identified (by being physically present) • Informed consent is obtained on treatment and processing of health data in context of mHealth program	• Consent for data processing is: freely given; specific; informed; and unambiguous	• Only sign up patients after a visit to the outpatient clinic in which patient is informed about HartWacht
1	Data collection	• Disclosure of relevant data stored and processed • Certification for data collectors	• Using a login with two-factor authentication • Legal position of company as data processor (and controller)	• Provide patients with validated and certified mobile applications of contracted partners • Fully automated integration between mobile application and hospital information system
2	Data transmission	• Data controller and data processor reach agreement about processor's activities and duties (data processing agreement, DPA)	• Applying highest level of encryption as described in IT-security guidelines • When involving cloud services: additional security and confidentiality risks	• DPA between CCN and manufacturers of devices and applications
3	Data storage on external servers	• Data processor provides appropriate technical and organizational measures to facilitate data processing according to data protection principles (such as data minimization) in accordance with DPA	• Storing health data on servers in countries outside EU, not providing adequate level of data protection	• Agreed with data processors to store the data in Netherlands and Ireland (EU)
4	Sharing of personal data	• Data are shared in line with purpose description in DPA, unless data are aggregated and no longer considered personal data in light of GDPR	• Sharing personal data for other purposes than initial description in DPA	• Sharing of data limited to the purpose described in the DPA, such as device distribution or generation of medical data

Table 4.1: ***Continued***

Phase	Element	Implications from data protection legislation (GDPR)	Points of attention	HartWacht learning points
5	Sharing of aggregated data	• Data are shared in line with purpose description in DPA, unless data are aggregated and no longer considered personal data in light of GDPR	• When using personal data for medical data research: not without consent or without meeting conditions of consent exemption	• Only data not considered personal data might be used for research purposes
6	Data storage by healthcare provider	• Hospital information system meets required security safeguards • Supervising Data Protection Officer (DPO) is appointed and a Data Privacy Impact Assessment (DPIA) is performed	• Duty to notify data breaches within 72 hours after discovery	• Making use of a hospital information system containing the appropriate ISO certifications • Repeating the DPIA for each structural change in HartWacht
7	Data interpretation by healthcare provider	• Designing the mHealth infrastructure for purposeful data processing (privacy by design and default)		• Limit data collection to relevant parameters: only blood pressure in the hypertension group, only EKG in the arrhythmia group

4. Sharing of personal data

Data processors (the companies that delivers the mHealth infrastructure) are required to minimize the data that are collected and limit it to what has been agreed on with the data controller (Article 28 paragraph 3 sub a GDPR). Processing of health data for purposes outside the professional healthcare domain (such as medical data research or product development or other commercial purposes) is strictly prohibited without prior consent.

5. Sharing of aggregated data

In the case of a mHealth infrastructure, aggregated and truly anonymized data do not fall within the scope of the GDPR and could be used for statistical purposes or medical data research. Data with information that can be attributed to an identifiable person is not considered anonymous but pseudonymized and therefore the GDPR does apply (Recital 26 GDPR). Pseudonymized data may only be used for these purposes after explicit informed consent (Article 6 paragraph 1 sub a GDPR and Article 9 paragraph 2 sub a GDPR).

6. Data storage by data controller

The HCP as data controller is required to maintain a record of all processed data in the mHealth program (Article 30 paragraph 1 GDPR) and use a hospital information system with adequate security safeguards. Other responsibilities include designating a data protection officer (DPO) (Article 37 GDPR) and executing data protection impact assessments (Article 35 GDPR). The tasks of the DPO are explicitly mentioned in the GDPR and include, among other things, to monitor compliance with the GDPR and cooperate with supervisory authority if necessary (Article 39 paragraph 1 GDPR). In the case of a personal data breach the healthcare institution should notify the local authority within 72 hours after discovery (Article 33 paragraph 1 GDPR).

7. Data analysis by HCP

In this phase of data processing, 'privacy by design' and 'privacy by default' are important principles (Article 25 GDPR). This means, for instance, that the mHealth program is designed in such a way that *only personal data which are necessary for each specific purpose of the processing are processed* (Article 25 paragraph 2 GDPR). Recognised certification can serve as an indicator to authorities that the data controller has complied with these requirements (Article 25 GDPR).

Compliance issues with data protection legislation healthcare providers should be aware of

As explained above, the GDPR has important consequences for the emerging field of mHealth whereas its functioning is largely dependent on the processing of health data; the presented 'roadmap' (see Figure 4.2 and Table 4.1) seeks to support healthcare providers who intend to set-up and implement a GDPR-compliant mHealth infrastructure. In this paragraph, we briefly discuss three issues related to complying with the GDPR.

Applicability of the GDPR

A first issue is whether data processing or certain parts fall within the scope of the GDPR. When data is truly anonymized the latter is not the case. In that situation, data may be processed by any party for any legitimate purpose, varying from commercial purposes to medical research or statistics. But the GDPR sets the bar high on anonymization, stating in Recital 26 GDPR that data is anonymous where it does 'not relate to an identified or an identifiable person'. Anonymization is a technique applied to personal data in order to achieve irreversible de-identification [13]. The same recital makes very clear that personal data which is 'only' pseudonymized, should be still considered to be information on an identifiable natural person. To determine whether a natural person is identifiable, (…) 'account should be taken of all the means reasonably likely to be used, such as singling out, either by the controller or by another person to identify the natural person directly or indirectly. To ascertain whether means are reasonably likely to be used to identify the natural person, account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration the available technology at the time of the processing and technological developments'.

However, the line between anonymous and personal data can, in practice, be difficult to draw. Therefore, we advise to be on the safe side: in case of doubt on the identifiability of the data, they should be considered to be personal non-anonymized data and fall within the scope of the GDPR.

Legal position of company providing mHealth

In general, the HCP is 'data controller', and the company that delivers the mHealth structure 'data processor'. This is an important distinction because the GDPR treats the two very differently. The data *controller*, determining the purposes and the nature of the data processing, is the principal accountable party and carries the main

responsibilities. The data processor merely performs certain activities with personal data, according to previously made contractual agreements with the data controller in a data processing agreement (DPA), and has, therefore, as its main GDPR-responsibility, to ensure an adequate level of security, suitable to the risk of data processing (Article 32 paragraph 1 GDPR). When a device- and application manufacturer simply carries out its assignment, it can be seen as a data processor. But if the company would do more with its collected patient data, for instance process these for commercial or research purposes, it needs to be regarded also as a (second) data controller according to the GDPR, implying that all corresponding duties for controllers apply. In the latter situation the company's responsibilities under the GDPR are much more extensive than in the first situation.

Involving cloud services

Because of their technical possibilities and flexibility, it may be profitable for data controllers and processors to involve *cloud services* in providing mHealth, for instance to obtain on-demand availability of data storage via the internet – the latter at relatively low costs and minimal maintenance activities. When a cloud service company is involved, this party would, similar to the device company, qualify as a data processor. How attractive this may be, the controller's and processor's joint responsibilities on appropriate security measures and safeguards should be assessed even more carefully in this setting. We aim especially at increased privacy and confidentiality risks, caused by, for instances, strict legislation on national security and terrorism in countries outside Europe, such as China and the United States. From privacy perspective, a cloud service based within the EU is preferable. An overview of the current involvement of cloud services in general healthcare does not exist, but a survey shows an adoption of 35% by HCP in the United States in 2016 of which 93% does not meet the standard of data security [14].

Final remarks

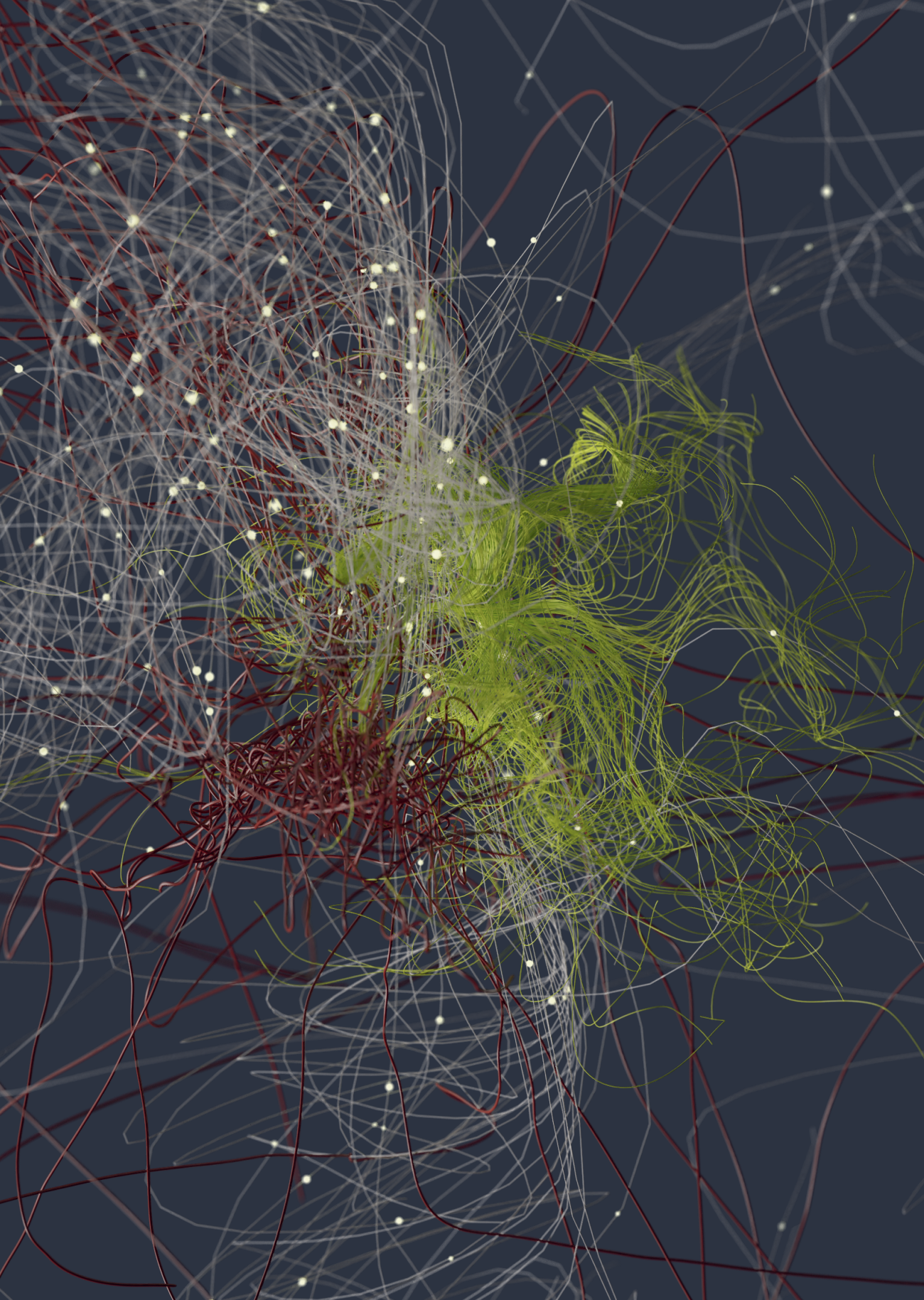
Innovative ways of healthcare delivery, such as medicine by mobile and wearable devices, seem very promising in improving quality of care at lower costs. Therefore, we should encourage them, but not without paying proper attention to the principles and requirements of data protection legislation. The GDPR was enforced in May 2018 to ensure data protection of all EU citizens. Just like in medical data research, there has to be a fair balance between data protection and data processing for legitimate purposes. In medical research this is progression of scientific knowledge, in mHealth

this is innovation that could lead to better quality of care for patients at lower costs [15]. The challenges and pitfalls we provide in this manuscript hopefully help healthcare providers starting mHealth initiatives to comply with its most important provisions. The mHealth specific Privacy Code of Conduct (2015), established by the European Commission [16] but yet to be approved [17], also gives practical guidance. The most important responsibility for healthcare providers is to inform patients on data processing and to obtain their explicit consent. Only by complying with these and other GDPR-provisions, mHealth can live up to its promises in the near future.

REFERENCES

1. *Green Paper on mobile health*. Brussels, https://ec.europa.eu/digital-single-market/en/news/green-paper-mobile-health-mhealth (2014).
2. World Health Organisation. eHealth. *eHealth Resolut to 58th Meet World Heal Assem* 2004; 121–123.
3. Cowie MR, Bax J, Bruining N, et al. e-Health: a position statement of the European Society of Cardiology. *Eur Heart J* 2016; 37: 63–66.
4. Kaewkannate K, Kim S. A comparison of wearable fitness devices. *BMC Public Health*; 16. Epub ahead of print 2016. DOI: 10.1186/s12889-016-3059-0.
5. Pevnick JM, Birkeland K, Zimmer R, et al. Wearable technology for cardiology: An update and framework for the future. *Trends Cardiovasc Med* 2018; 28: 144–150.
6. Maric B, Kaan A, Ignaszewski A, et al. A systematic review of telemonitoring technologies in heart failure. *Eur J Heart Fail* 2009; 11: 506–517.
7. Habbig A-K, Quinn P, De Hert P, et al. The Data Protection and Medical Device Frameworks — Obstacles to the Deployment of mHealth across Europe? *Eur J Health Law* 2013; 20: 185–204.
8. European Union. *Regulation 2016/679*. 2016. Epub ahead of print 2016. DOI: http://eur-lex.europa.eu/pri/en/oj/dat/2003/l_285/l_28520031101en00330037.pdf.
9. Wierda E, Eindhoven DC, Schalij MJ, et al. Privacy of patient data in quality-of-care registries in cardiology and cardiothoracic surgery: the impact of the new general data protection regulation EU-law. *Eur Hear J - Qual Care Clin Outcomes* 2018; 4: 239–245.
10. McCall B. What does the GDPR mean for the medical community? *Lancet (London, England)* 2018; 391: 1249–1250.
11. *ANNEX - health data in apps and devices*, https://ec.europa.eu/justice/article-29/documentation/other-document/files/2015/20150205_letter_art29wp_ec_health_data_after_plenary_annex_en.pdf (accessed 14 February 2019).
12. Botrugno C. Telemedicine in daily practice: Addressing legal challenges while waiting for an EU regulatory framework. *Heal Policy Technol* 2018; 7: 131–136.
13. DATA PROTECTION WORKING PARTY. *Opinion 05/2014 on Anonymisation Techniques,* http://ec.europa.eu/justice/data-protection/index_en.htm (2014).
14. McAfee. *Cloud adoption and Risk Report*. 2019.
15. Ploem MC, Essink-Bot ML, Stronks K. Proposed EU data protection regulation is a threat to medical research. *BMJ* 2013; 346: f3534–f3534.

16. European Commission. Privacy Code of Conduct on mobile health apps, https://ec.europa.eu/digital-single-market/en/privacy-code-conduct-mobile-health-apps (2018).
17. Graux H. *Article 29 Data Protection Working Party*. Brussels, 2018.



Chapter 5

The accuracy of heartbeat detection using photoplethysmography technology in cardiac patients

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ABSTRACT

Introduction: Photoplethysmography (PPG) in wearable sensors potentially plays an important role in accessible heart rhythm monitoring. We investigated the accuracy of a state-of-the-art bracelet (Corsano 287) for heartbeat detection in cardiac patients and evaluated the efficacy of a signal qualifier in identifying medically useful signals.

Methods: Patients from an outpatient cardiology clinic underwent a simultaneous resting ECG and PPG recording, which we compared to determine accuracy of the PPG sensor for detecting heartbeats within 100 and 50 ms of the ECG-detected heart beats and correlation and Limits of Agreement for heartrate (HR) and RR-intervals. We defined subgroups for skin type, hair density, age, BMI and gender and applied a previously described signal qualifier.

Results: In 180 patients 7,914 ECG-, and 7,880 (99%) PPG-heartbeats were recorded. The PPG-accuracy within 100 ms was 94.6% (95% CI 94.1-95.1) and 89.2% (95% CI 88.5-89.9) within 50 ms. Correlation was high for HR (R = 0.991 (95% CI 0.988-0.993), n = 180) and RR-intervals (R = 0.891 (95% CI 0.886-0.895), n = 7,880). The 95% Limits of Agreement (LoA) were -3.89 to 3.77 (mean bias 0.06) beats per minute for HR and -173 to 171 (mean bias -1) for RR-intervals. Results were comparable across all subgroups. The signal qualifier led to a higher accuracy in a 100 ms range (98.2% (95% CI 97.9-98.5)) (n = 143).

Conclusion: We showed that the Corsano 287 Bracelet with PPG-technology can determine HR and RR-intervals with high accuracy in cardiovascular at-risk patient population among different subgroups, especially with a signal quality indicator.

INTRODUCTION

Cardiovascular disease (CVD) is among the leading causes of mortality globally with approximately 17 million deaths annually, a number growing to up to 23 million by 2030 [1]. To minimize complications of CVD, early detection of cardiac disorders, such as arrhythmias, is critical. The electrocardiogram (ECG) is considered the golden standard for arrhythmia detection, but its application is limited to the clinical setting, making concurrent recording with an episode of symptoms challenging [2]. Additionally, arrhythmias such as atrial fibrillation (AF) are often asymptomatic and potentially remain undetected until complications, such as thromboembolic events, occur [3].

Therefore, continuous heart rhythm monitoring is beneficial, especially in at-risk cardiac patients [4]. Current devices for continuous monitoring, such as ambulatory ECG (AECG) recorders and implantable loop recorders (ILR), have their limitations, as AECG recorders are burdensome to wear and provide only limited recording time (24-72 hours), while ILRs are invasive and costly [4,5].

As an alternative, the use of wearable devices for recording vital parameters through sensors enables mobile diagnostics by supplying data on the cardiovascular status of a patient at home. These smartphone-based solutions enable efficient and easy screening, and may reduce complications of cardiovascular disease through early detection of anomalies and appropriate therapeutic intervention [6]. Recent advances in photoplethysmography (PPG) have produced a new class of wearable devices for continuous and long-term health data acquisition and monitoring [7,8].

Previous research on the application of smart devices with sensor technology either focused on large consumer populations without selection for at-risk participants [9] or is applied on a limited number of patients at risk of cardiac arrhythmias [3,10]. Additionally, there has been limited attention on the impact of subject characteristics, such as skin type, hair density and body mass index, on PPG accuracy and of external disturbances such as ambient light or movement on PPG signal quality [11–15]. Because of the variance in signal quality, a signal qualifier can be applied to remove low quality parts of PPG recordings, with the aim of producing data with medical precision that is usable in clinical practice [15].

In this study, we aimed to evaluate the accuracy of a wrist-worn PPG device (Corsano CardioWatch/Bracelet 287) for pulse detection in a varied group of cardiovascular patients in a real-life outpatient setting, taking subject characteristics into account. Furthermore, we evaluated the efficacy of a signal qualifier for identifying medically useful signals.

METHODS

Study design and patient selection

In this single-centre prospective study, we assessed the accuracy of pulse detection using Corsano CardioWatch 287 (the Corsano Watch 287 or the Corsano Bracelet 287, Corsano Health B.V. Bussum, The Netherlands), determined its accuracy among pre-specified subgroups and applied a signal qualifier to determine its added value. The study population consisted of cardiac patients referred by their general practitioners to one of the outpatient clinics of Cardiology Centers of the Netherlands. All patients scheduled for a resting-ECG were included consecutively based on the inclusion- and exclusion criteria. Patients < 18 years or with pacemaker dependent rhythm were excluded from the study.

The primary outcome of the study was the accuracy of the PPG-signal compared to a 12-lead resting ECG, defined as the proportion of correctly detected heartbeats by PPG within 100 ms and within 50 ms of the ECG registration. In addition, we determined the correlation (r) and the 95% Limits of Agreement (LoA) between ECG and PPG for HR and RR-intervals. We determined accuracy of the PPG-signal among subgroups separately and constructed a linear regression model to evaluate the influence of patient characteristics on the accuracy of RR-intervals. The absolute difference of RR-intervals in milliseconds between PPG and ECG was defined as the dependent variable.

RR-interval determination is sensitive to signal quality fluctuations. Therefore, besides analysing RR-interval accuracy for the whole study population, we also analysed RR-interval accuracy for a subgroup of patients whose measurements scored no less than 80% on the index. Since the determination of HR is based on the total number of detected heartbeats and is to a much lesser extent dependent on high RR-interval determination accuracy, we considered applying the signal qualifier to the analysis of HR accuracy as clinically irrelevant.

Cardiovascular history, and body height and weight were registered. Skin type was determined for each patient according to the Fitzpatrick classification, ranging from skin type I (pale white skin) to type VI (dark brown or black skin) [16]. Hair density was graded into four categories by comparing the forearm of the participant to a set of previously described set of photographs, ranging from nil to dense [17]. Subgroups were defined by gender, age, BMI, skin colour, hair density and atrial fibrillation (AF). Age was segmented into cohorts of 10 years. BMI > 25 was defined as overweight. Skin

levels IV, V and VI were considered dark. Hair density 'moderate' and 'dense' were considered increased.

To determine the quality of the recordings, we applied a signal qualifier that has been described in previous research [15]. This method calculates the normalized cross-correlation coefficient of each signal segment with a reference signal. Then, it non-linearly scales the coefficient to a signal quality index (SQI) ranging from 0 to 100%, where 0% indicates the poorest, and 100% the highest signal quality. For each recording, the mean SQI was calculated.

Participants agreed to participate in the study by signing written informed consent before inclusion. The study was approved by the institutional ethics committee of Amsterdam University Medical Centre. The trial was registered at www.trialregister.nl under reference number NL8866.

Data acquisition

For each participant, measurements of PPG and ECG were simultaneously recorded for 45 seconds. The PPG-device was started several seconds before and ended after several seconds the ECG-device registration. Participants were at rest and supine on an exam table with their arms resting on a steady surface and were instructed not to move or speak during the measurements for quality optimisation of the recordings.

The PPG-wearables were wirelessly connected to an Android smartphone running dedicated software. The data was transmitted from the bracelet to the smartphone via a Bluetooth Low Energy (BLE) connection. From the smartphone the raw PPG data were transferred to a cloud server and forwarded to the cloud-based application for analysis.

The 12-lead ECGs were acquired by a Welch Allyn Pro resting ECG Recorder (Skaneateles Falls, New York, USA). Raw ECG data were exported to a cloud server.

Data processing

RR-intervals from both the PPG signal and the ECG signal were determined by an algorithm implemented in MATLAB version R2020b (MathWorks, Massachusetts USA). The PPG-signal was denoised by applying a 0.6-5.0 Hz band-pass filter. The individual heartbeats were detected by automated peak detection. R-peaks were determined from the ECG signal by automated peak detection. For both the PPG and ECG signal, the RR-intervals were subsequently calculated and stored in an array,

with one array for each signal. The signals were then synchronized by determining the time lag with the least error between both arrays, enabling the matching of every PPG heartbeat to an ECG heartbeat. Non-matching PPG heartbeats were automatically matched to the closest ECG heartbeat. Figure 5.1 shows a typical synchronized PPG and ECG measurement.

Sample size

We performed a sample size calculation to guarantee sufficient power for establishing accuracy in terms of the proportion PPG heartbeats within 100 ms of ECG heartbeats. The calculation was done with PASS (version 15.0.2) for two-sided exact Clopper-Pearson 95% confidence intervals for one proportion. Recording in 150 patients with an average heart rate of 60 bpm for 45 seconds, yielding 6,750 heartbeats, produces a two-sided 95% confidence interval with a width equal to 0.015 and a lower limit of the 95% confidence interval of 0.893 when the sample proportion is 0.900. We added 20% as a buffer and aimed for a study population of 180 participants.

Statistical analysis

The HR metrics and the beat-to-beat intervals derived from the PPG-signal were compared with the HR and RR length of corresponding windows of the ECG signal. The accuracy was assessed by a Pearson's correlation and Bland Altman plots with multiple observations correction for Limits of Agreement, and measurements of the proportion of accurately detected measurements. We determined the proportion of PPG detected heartbeats within 100 ms of ECG measurements as primary outcome. We additionally established the proportion of PPG measurements within 50 ms of ECG measurements, the Pearson correlation between PPG and ECG HR and RR-intervals, and 95% (LoA) between PPG and ECG HR and RR-intervals. P-values were considered significant when $p < 0.05$. All results are shown as n (%), Mean ± Standard deviation or Median (IQR) if not normally distributed.

RESULTS

Participant demographics

The study population consisted of 180 participants (participants (60 ± 15 years old, 80 (44%) female). Participants were patients suspected for cardiovascular disease according to complaints, medical history and the presence of cardiovascular risk

factors. The skin type heterogeneity was limited, as 74% of the participants were classified with a cream white skin (Fitzpatrick type III). The hair density (scored as nil, sparse, moderate) varied among the participants, with a slight predominance of sparse. Table 5.1 displays the baseline characteristics of the participants.

Table 5.1: Participant characteristics

n	180
Characteristics	**Value**
Female (%)	80 (44)
Age [years] (mean ± SD)	60 ± 15
BMI [kg/m^2] (mean ± SD)	27.0 ± 5.0
General cardiac history	**n (%)**
Ischemic heart disease	83 (46)
Heart failure	3 (2)
Other	54 (30)
None	17 (9)
History of cardiac arrhythmia	**n (%)**
Paroxysmal atrial fibrillation	31 (17)
Persistent atrial fibrillation	10 (6)
Atrial flutter	2 (1)
Other supraventricular arrhythmia	18 (10)
Ventricular arrhythmia	13 (7)
Conduction disorders	2 (1)
Risk factors	**n (%)**
Hypertension	60 (33)
Diabetes	13 (7)
Dyslipidemia	27 (15)
Fitzpatrick score	**n (%)**
Type I	2 (1)
Type II	20 (11)
Type III	133 (74)
Type IV	11 (6)
Type V	12 (7)
Type VI	2 (1)
Hair density	**n (%)**
Nil	50 (28)
Sparse	67 (37)
Moderate	42 (23)
Dense	21 (12)

BMI - Body mass index. Cardiac history classified as Other: heart valve abnormalities, vascular disorders, structural abnormalities of the heart, pericarditis, aortic valve plastics and carotid stenosis Fitzpatrick scores - type I, pale white; type II, white; type III, cream white; type IV, moderate brown; type V, dark brown; and type VI, deeply pigmented dark brown. Hair density - nil, sparse, moderate and dense.

PPG accuracy

In 180 patients a total of 7,914 ECG beats were recorded and 7,880 (99%) were also recorded by PPG. Figure 5.1 displays an example of a 45 second PPG and ECG measurement. The PPG-accuracy, defined as the proportion of PPG measurements within 100 ms of ECG measurements, was 94.6% (95% CI 94.1-95.1). The accuracy within 50 ms range was 89.2% (95% CI 88.5-89.9). Correlation was high for HR (R = 0.991 (95% CI 0.988-0.993), n = 180) (Figure 5.2A). The 95% Limits of Agreement (LoA) were -3.89 to 3.77 (mean bias -0.06) beats per minute (Figure 5.2B). For the RR-intervals, correlation was similarly high (R = 0.891 (95% CI 0.886-0.895), n = 7880) (Figure 5.3A). The 95% LoA for RR-intervals were -173 to 171 (mean bias -1) ms (Figure 5.3B).

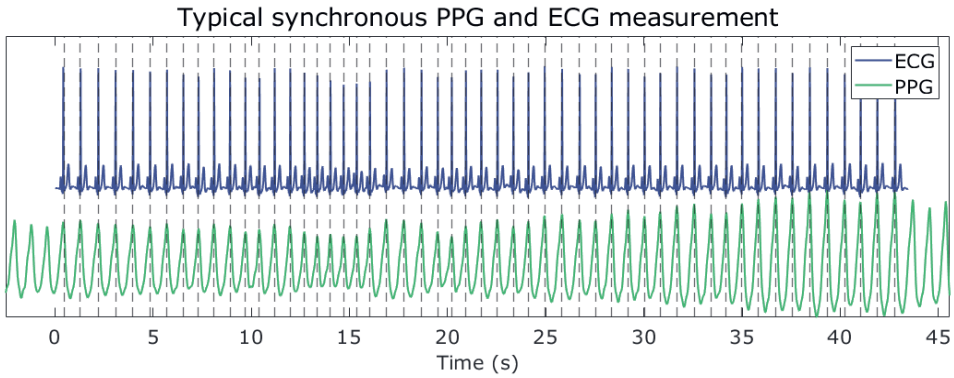

Figure 5.1: Simultaneous recordings of PPG and ECG data.
PPG measurement was started before and ended after the ECG registration. Non-matching PPG heartbeats were automatically matched to the closest P-top on the ECG-signal.

Subgroup analysis

Subgroup analysis demonstrated statistically significant, yet low coefficients for gender, age and BMI and AF (Table 5.2). Female gender yields the most divergence between PPG and ECG measurements (7.45 ms, 95% CI 2.70 to 12.22), followed by age (5.91 ms per 10 years increment, 95% CI 4.67 to 7.16). Higher BMI results in less divergence between PPG and ECG (-7.34 ms, 95% CI -11.08 to -6.12). The magnitude of the divergence was small for all parameters.

Subgroup analysis for the categorical variables (gender, BMI, skin type and hair density) showed comparable accuracy among all subgroups (see appendix A-D).

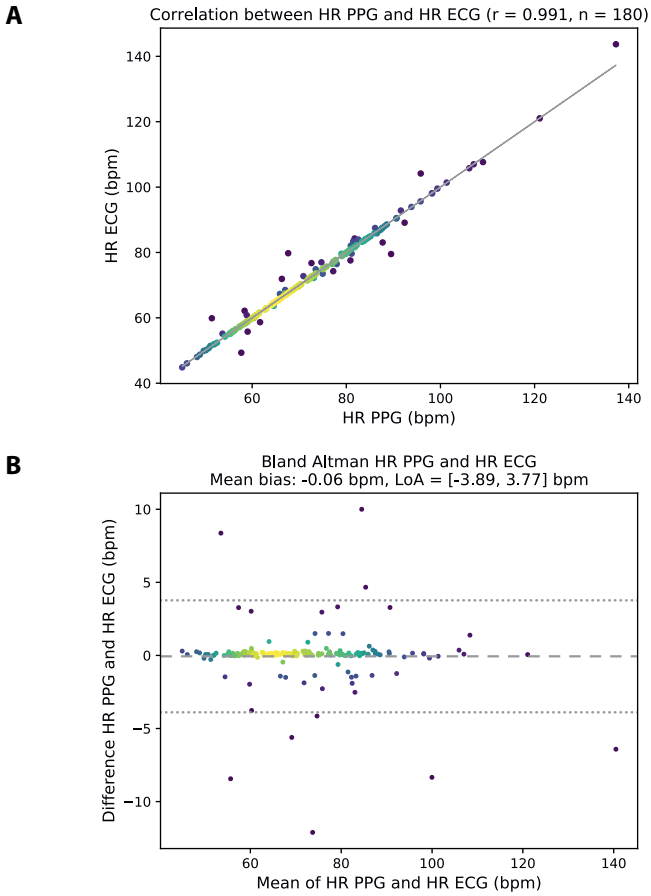

Figure 5.2: A. Correlation of HR-determination (beats per minute) between PPG and ECG. **B.** Limits of Agreement (LoA) of HR-determination between PPG and ECG, the 95% LoA are marked by the dotted lines.

Signal quality indicator

The median signal quality indicator of the recordings was 94% (IQR 85-100). From the total set of recordings (n = 180), 37 (20%) were classified with an SQI < 80% and excluded for this analysis, leading to a new subgroup of 144 high-quality measurements. In this group, a total of 6,165 ECG beats were recorded and 6,139 (99%) were also recorded by PPG. The accuracy of the PPG-signal in a 100 ms range from the ECG measurement was superior and showed to be 98.2% (95% CI 97.9-98.5). The RR-intervals on the PPG were highly correlated with those on the ECG (R = 0.966 (95% CI 0.964-0.968), n = 6,139) (Figure 5.4A), with a narrow 95% LoA of -85 to 85 (mean bias -1) ms (Figure 5.4B).

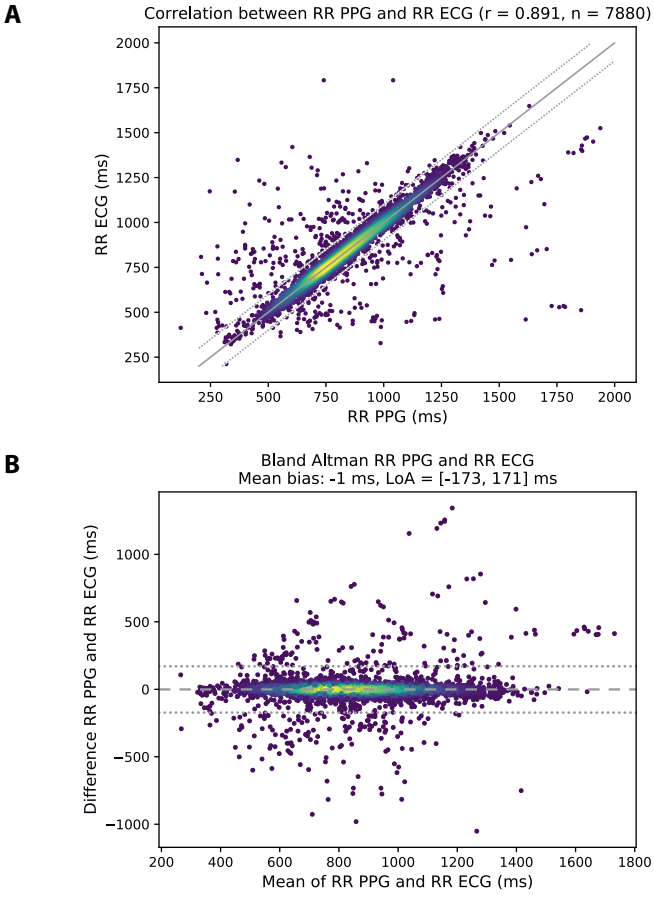

Figure 5.3: A. Correlation of determined RR-intervals between PPG and ECG; the +/- 100 ms range is marked by the dotted lines. **B.** Limits of Agreement (LoA) of determination of RR-intervals between PPG and ECG; the 95% LoA are marked by the dotted lines.

Table 5.2: Linear regression for absolute ECG-PPG difference

Parameter	Coefficient (ms) [95% CI]	P-value
Model intercept	-0.93 [-0.96 - 7.79]	0.834
Female gender	7.45 [2.70 - 12.22]	0.002*
Age (10-year increments)	5.91 [4.67 - 7.16]	< 0.001*
High BMI	-7.34 [-11.08 - -6.12]	< 0.001*
Dark skin type	-2.33 [-7.69 - 3.02]	0.393
Dense hair type	-0.23 [-5.26 - 4.80]	0.929

BMI: Body Mass Index. (*) denotes statistical significance.

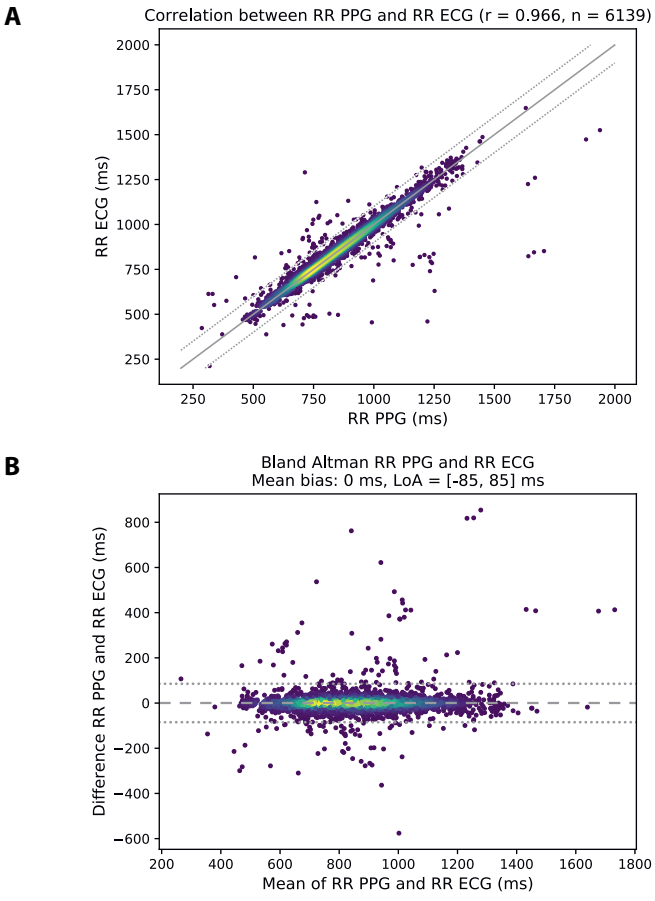

Figure 5.4: A. Correlation of determined RR-intervals between PPG and ECG, after excluding low quality data; the +/- 100 ms range is marked by the dotted lines. **B.** Limits of Agreement (LoA) of determination of RR-intervals between PPG and ECG, the 95% LoA are marked by the dotted lines.

DISCUSSION

We analysed the accuracy of the Corsano 287 bracelet and watch using PPG-technology for detecting heart beats and measuring HR and RR-intervals in comparison with ECG as a golden standard. We observed an accurate heartbeat detection and determined a high correlation between PPG signals and ECG recordings when measuring HR and RR-intervals in an at-risk study population. This indicates that the current device could benefit our cardiovascular patient population. Divergence between PPG and ECG differed slightly among predefined subgroups; however, discrepancies were small and unlikely to be clinically relevant. Applying a signal qualifier led to an increase in accuracy

of the PPG-signal, paving the way for potential future use in daily clinical practice for detection of AF. Early detection of AF is essential, as preventive anticoagulation therapy significantly reduces risk of complications such as stroke and death [18]. In addition to diagnostic purposes, wearable devices with PPG-technology are specifically suited for long term remote monitoring of patients already diagnosed with arrhythmias. Current remote monitoring programs are mainly symptom-driven, continuous monitoring with PPG-technology would add possibilities for asymptomatic patients [19].

PPG devices using incorporated software algorithms have been studied in comparison to traditional 12-lead ECG devices, showing that data from 12-lead ECG recordings and the pulse rate variability based on photoplethysmographic correlate between 0.94 and 0.99 for HR estimates [3,6,10]. The large majority of these data were established in a consumer (i.e. non-clinical) setting, but it was anticipated that the diagnostic benefit of these devices is high, especially in patients with cardiovascular diseases. Accuracy of PPG devices in comparison to ECG recordings is generally defined as the proportion of PPG measurements within 100 ms of ECG measurements [3,14]. In addition to this usual definition, we show that a stricter range of 50 ms leads to a slight decrease of accuracy, as more PPG-detected heartbeats are defined as inaccurate for being outside of this range. For future research with improving PPG-technology, high accuracy within a narrow range of 50 ms should be pursued.

Our results are in keeping with previous research that showed considerable accuracy of the PPG signal for pulse detection, specifically when recorded at rest [6,10,20]. Our study adds to this knowledge by establishing a high accuracy in a relatively large and heterogenous cohort of cardiovascular patients in a real-life outpatient cardiology clinic. Since these patients may ultimately benefit from continuous heart rhythm monitoring, establishing its accuracy in this specific setting is paramount.

We determined overall 95% LoA for HR to be -3.89 to 3.77 (mean bias 0.06) beats per minute (bpm). This is well within the maximal allowable error ± 5 bpm for heart rate meters as described by the Association for the Advancement of Medical Instrumentation [21]. The agreement was high for all subgroups, although we found slight yet significant differences among them. The highest magnitude of the divergence between PPG and ECG was 7.45 ms for female gender, (95% CI 2.70 to 12.22) which is likely not to be of clinical significance, as was the magnitude for age. We found that in our study, higher BMI is correlated with a slightly higher accuracy, while the opposite was expected. This higher accuracy may be caused by a tighter fit of the bracelet on the wrist, preventing ambient light introducing noise on the sensor.

We additionally demonstrate the added value of the application of a signal qualifier to increase reliability of the RR-interval measurements. A range of external variables, such as interference from electrical devices or movement of the subject, can influence the quality of the PPG-signal [15]. For PPG-technology to eventually base clinical decision-making on, excluding low-quality episodes is crucial for achieving medical precision. By applying a previously described signal qualifier, accuracy within 100 ms range increased from 94.6% (95% CI 94.1-95.1) to 98.2% (95% CI 97.9-98.5).

To further develop the PPG-technology and make it suitable for usage in clinical practice, future research should focus on the impact of movement and activity on the accuracy of the PPG-signal, and on the application of algorithms to analyse heart rate variability and detect arrhythmias such as AF.

Strengths and limitations

In this study we analysed a large and heterogenous patient population, taking additional confounders such as risk factors, BMI, skin type and hair density into account, increasing the external validity of our study. From these confounders, skin type was unevenly distributed, as 74% of the participants was classified as type 3. This overrepresentation may limit generalizability of our results for other skin types.

All recordings in the trial were performed on patients at rest. It is therefore unknown whether the wearable and algorithm will produce similar results in an unsupervised ambulant setting. Other studies have shown that movement and physical exercise influence the quality of PPG recordings in a similar way as ECG 6,20. Hence, future studies should evaluate the current device under dynamic circumstances.

Additionally, recordings were relatively short, about 45 seconds. As the PPG-signal requires a "start-up phase" in which the signal is seeking to detect pulse, this short recording period may have led to a relatively lower accuracy. It can be anticipated that in patients who are monitored for a longer time at rest, the accuracy of the PPG recording will be higher. The short recording time also forced us to discard complete recordings with a low signal quality score for the signal quality subgroup analysis, instead of removing low quality parts within single recordings, as it would not leave sufficient RR-intervals for analysis. In longer recordings, the signal quality indicator can typically be used to remove low quality segments within one patient's measurement to increase the overall quality and accuracy of PPG derived parameters such as RR-intervals, rather than deleting a complete record.

Conclusion

This validation study showed that the Corsano 287 CardioWatch/Bracelet with PPG-technology can determine HR and RR-intervals with high accuracy in a cardiovascular patient population, with high quality output in different subgroups, especially when combined with a signal quality indicator. Due to their non-intrusive and convenient nature, wearable devices like these have great potential for high volume accessible long-term monitoring at-risk cardiac patients.

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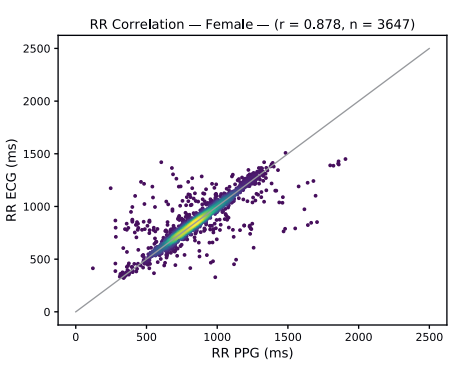
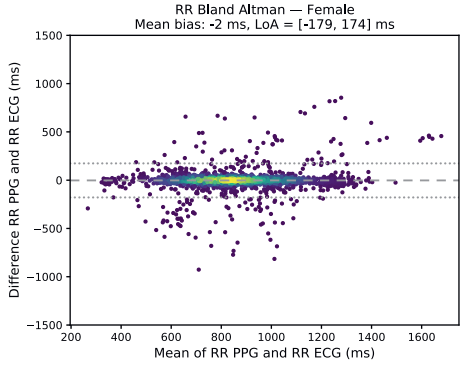
REFERENCES

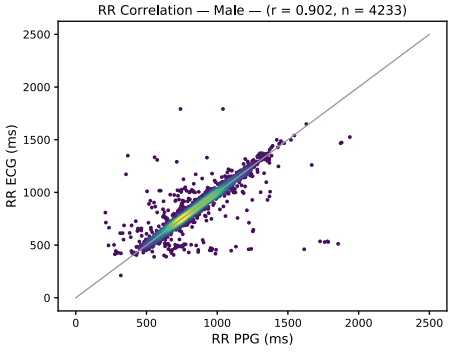
1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics—2009 Update. *Circulation*; 119. Epub ahead of print 27 January 2009. DOI: 10.1161/CIRCULATIONAHA.108.191261.
2. Ashrafuzzaman M, Mazaharul Huq M, Chakraborty C, et al. Heart Attack Detection Using Smart Phone. *Int J Technol Enhanc Emerg Eng Res* 2013; 1: 23–27.
3. Hochstadt A, Chorin E, Viskin S, et al. Continuous heart rate monitoring for automatic detection of atrial fibrillation with novel bio-sensing technology. *J Electrocardiol* 2019; 52: 23–27.
4. Diederichsen SZ, Haugan KJ, Kronborg C, et al. Comprehensive Evaluation of Rhythm Monitoring Strategies in Screening for Atrial Fibrillation. *Circulation* 2020; 141: 1510–1522.
5. Selder J, Proesmans T, Breukel L, et al. Assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data. *Comput Methods Programs Biomed* 2020; 197: 105753.
6. Koenig N, Seeck A, Eckstein J, et al. Validation of a New Heart Rate Measurement Algorithm for Fingertip Recording of Video Signals with Smartphones. *Telemed e-Health* 2016; 22: 631–636.
7. Dur O, Rhoades C, Ng MS, et al. Design Rationale and Performance Evaluation of the Wavelet Health Wristband: Benchtop Validation of a Wrist-Worn Physiological Signal Recorder. *JMIR mHealth uHealth* 2018; 6: e11040.
8. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas* 2007; 28: R1–R39.
9. Perez M V., Mahaffey KW, Hedlin H, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; 381: 1909–1917.
10. Hochstadt A, Havakuk O, Chorin E, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. *J Electrocardiol* 2020; 60: 138–141.
11. Fallow BA, Tarumi T, Tanaka H. Influence of skin type and wavelength on light wave reflectance. *J Clin Monit Comput* 2013; 27: 313–317.

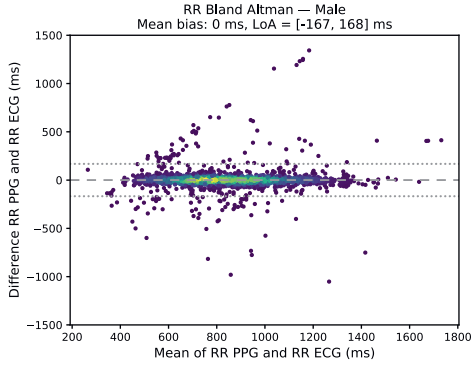
12. Boonya-ananta T, Rodriguez AJ, Ajmal A, et al. Synthetic photoplethysmography (PPG) of the radial artery through parallelized Monte Carlo and its correlation to body mass index (BMI). *Sci Rep* 2021; 11: 2570.
13. Sañudo B, De Hoyo M, Muñoz-López A, et al. Pilot Study Assessing the Influence of Skin Type on the Heart Rate Measurements Obtained by Photoplethysmography with the Apple Watch. *J Med Syst* 2019; 43: 195.
14. Hochstadt A, Havakuk O, Chorin E, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. *J Electrocardiol* 2020; 60: 138–141.
15. Li H, Huang S. A High-Efficiency and Real-Time Method for Quality Evaluation of PPG Signals. *IOP Conf Ser Mater Sci Eng* 2020; 711: 012100.
16. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988; 124: 869–871.
17. von Schuckmann LA, Hughes MC, Green AC, et al. Forearm hair density and risk of keratinocyte cancers in Australian adults. *Arch Dermatol Res* 2016; 308: 617–624.
18. Bordignon S, Corti MC, Bilato C. Atrial fibrillation associated with heart failure, stroke and mortality. *J Atr Fibrillation* 2012; 2: 53–61.
19. Kolk MZH, Blok S, De Wildt MCC, et al. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal*. Epub ahead of print 9 March 2021. DOI: 10.1093/ehjdh/ztab030.
20. Schäfer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability? *Int J Cardiol* 2013; 166: 15–29.
21. ANSI/AAMI. *Cardiac Monitors, Heart Rate Meters, and Alarms*. Arlington, 2002.

APPENDIX A - SUB ANALYSIS GENDER









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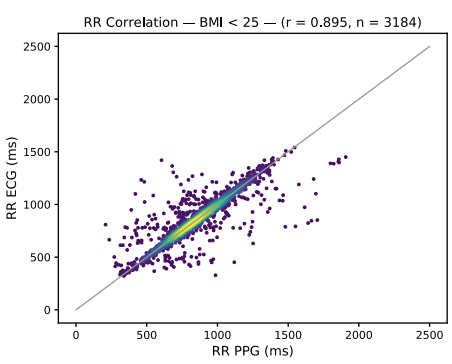

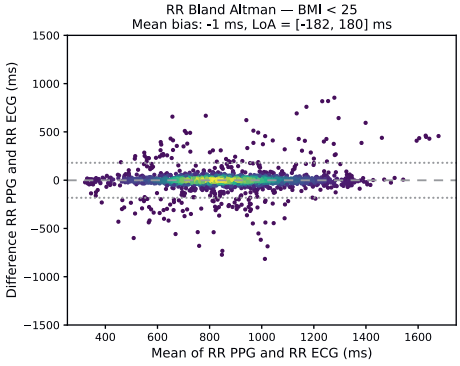

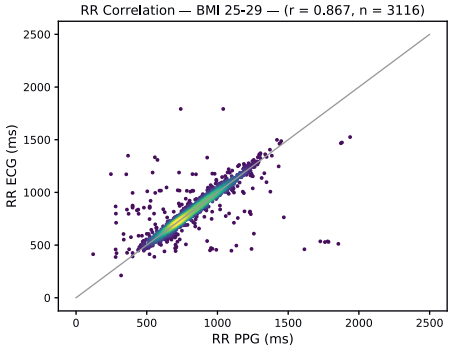

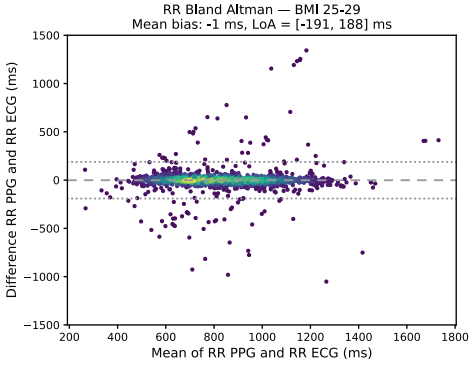

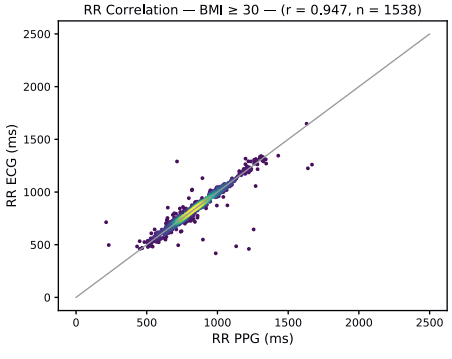

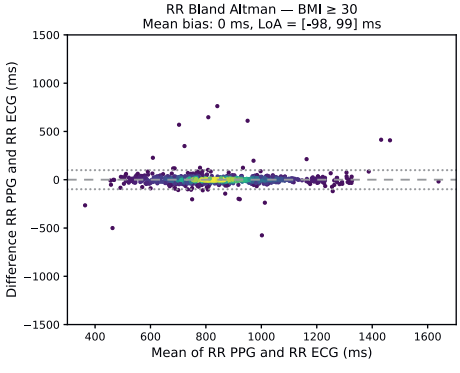

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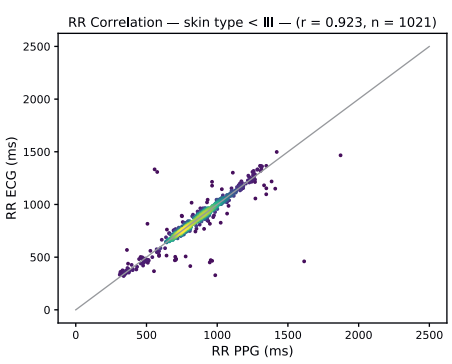

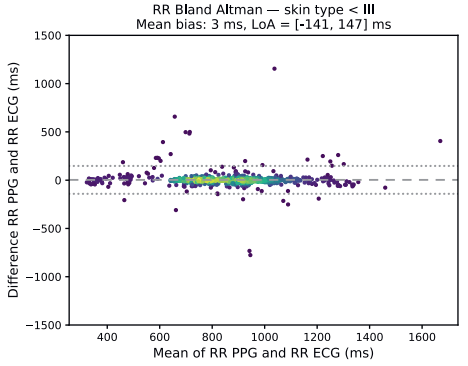

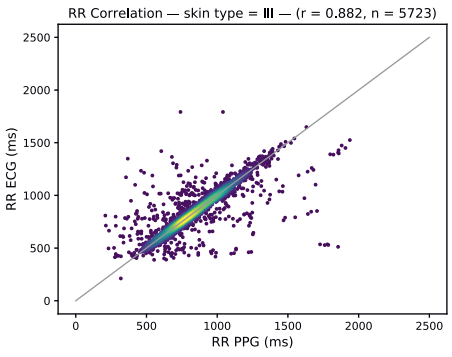

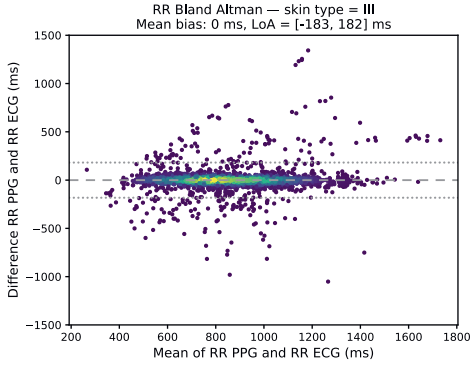

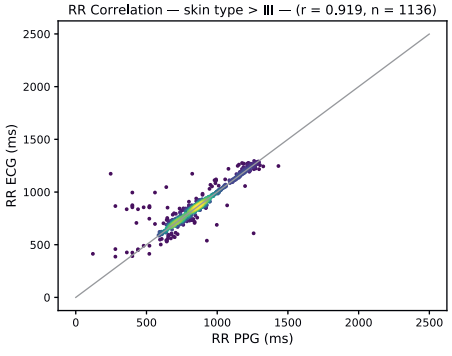

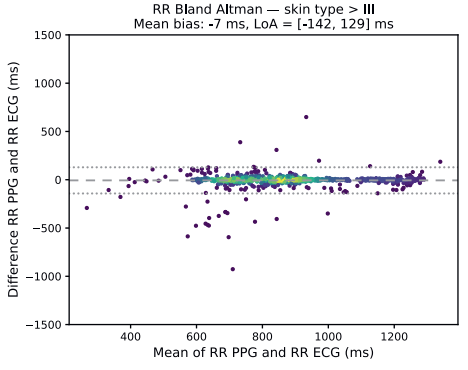

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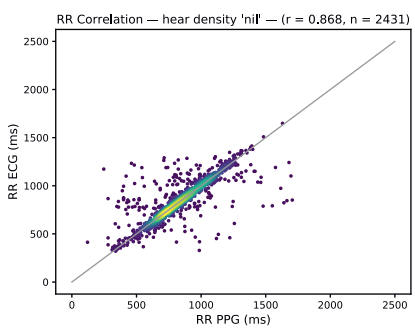

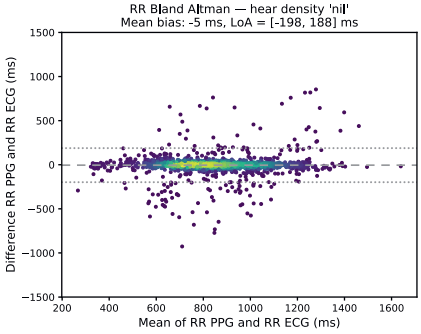

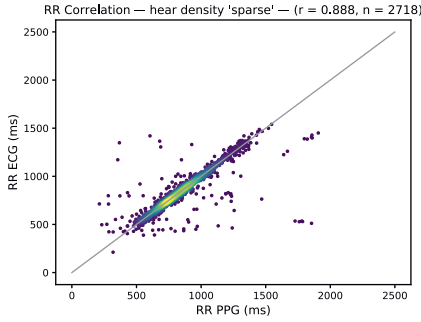

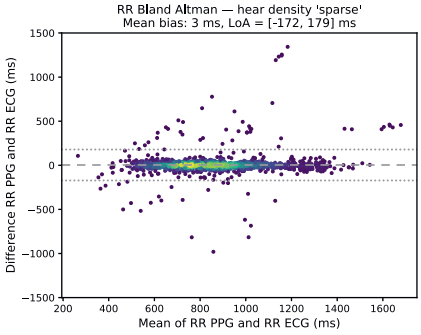

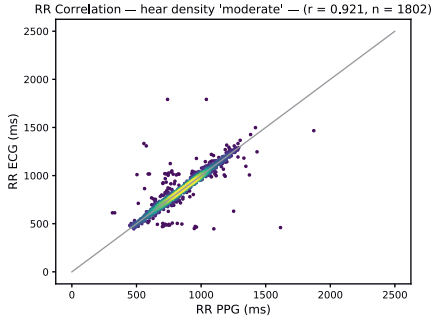

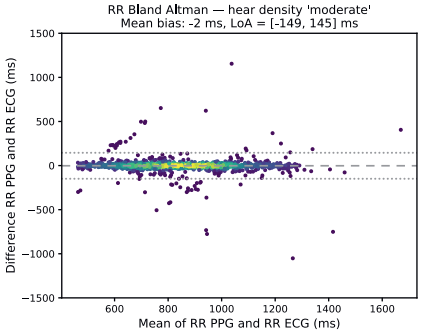

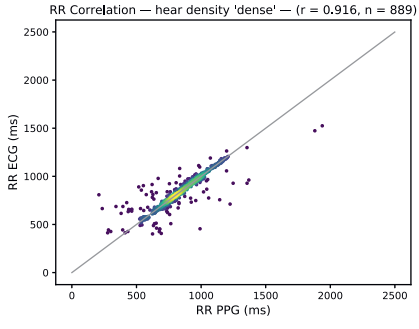

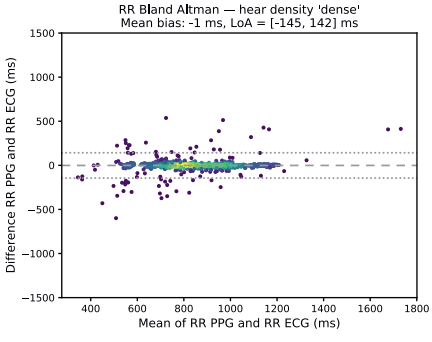

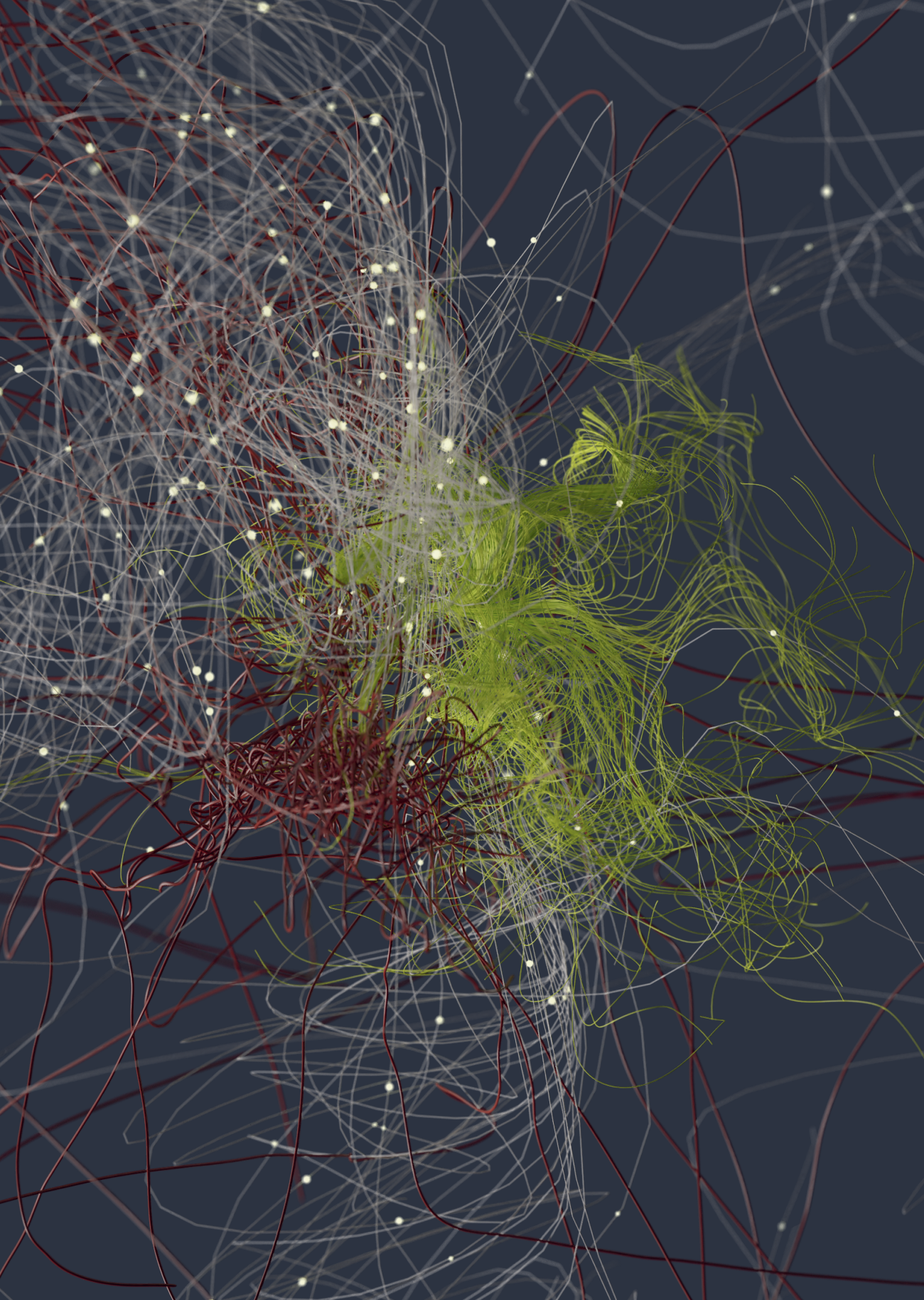

Chapter 6

Optimizing eHealth protocols for hypertension: lessons from the Dutch HartWacht program

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Bert-Jan H. van den Born

Submitted – Int J Med Inform

ABSTRACT

Introduction: eHealth, such as remote monitoring programs for the management of hypertension, can contribute to achieving blood pressure control. However, it has not yet been implemented in daily practice on large scale, partly due to the workload resulting from large amounts of patient generated data and subsequent notifications that need handling by a remote team.

Methods: We evaluated two protocols for handling of incoming eHealth data and compared them with respect to the number of notifications, clinically relevant alarms and corresponding workload. We used real-world data from the Dutch remote monitoring program HartWacht.

Results: 169 patients (63 ± 10 years old, 43% female) generated 10,225 home measurements. In protocol A this resulted in 2,331 (22%) notifications, with a corresponding workload of 76.5 hours, of which 68% was spent on clinically relevant handling. Protocol B resulted in 933 notifications that were all clinically relevant, with a corresponding workload of 52.7 hours, resulting in a decrease of the total workload of 31% in protocol B.

Conclusion: In remote monitoring programs for eHealth, relatively simple adjustments in protocols for automatic handling of patient-generated data can have considerable impact on workload for remote healthcare teams. Such automatization is essential for increasing scalability and accessibility of eHealth programs.

INTRODUCTION

In Europe 45% of deaths is caused by cardiovascular diseases (CVD), of which 58% is related to hypertension, its most important modifiable risk factor [1]. Blood pressure management, consisting of lifestyle advice often combined with medication, is crucial to prevent cardiovascular diseases. Treatment duration is often lifelong and requires chronic adherence to lifestyle advice and medication to bring BP to target. eHealth services have been shown to contribute to improved blood pressure control [2–6]. Through eHealth services physicians can be better informed about the effects of medication and lifestyle adjustment compared to infrequent physical patient visits, which may result in better regulation of blood pressure and subsequent clinical outcome for the patient. While evidence on cost-effectiveness of such programs is heterogeneous, success factors such as a high volume of connected patients, personalized feedback and partial replacement of usual care have been identified in earlier research [7].

Despite their potential, eHealth concepts often fail to succeed [8,9]. Important culprits are poor alert prioritization, inadequate user customization, lack of Electronic Health Record (EHR) integration and large data flow generated by patients. These factors contribute to high costs and increased workload of eHealth platforms [10].

An example of a remote monitoring infrastructure for patients with cardiovascular diseases is the Dutch HartWacht program. The HartWacht program is initiated in 2016 and fully reimbursed and integrated in daily clinical practice in outpatient clinics throughout the Netherlands [11–13]. Compared to traditional care models in which health parameters are only collected at visits to the outpatient clinic, for HartWacht participants much more data is structurally collected and stored in the patient record. To remotely interpret the incoming data and instantly react upon deviating measurements, a remote healthcare team ("eHealth Team") aided by smart algorithms has been set up.

The scalability of eHealth systems such as HartWacht predominantly depends on the time healthcare professionals spend on manual verification and handling of the incoming data. Especially notifications that require verification but are not followed by an action, such as contacting the patient or changing medical strategy, hamper efficient upscaling and inhibit implementation. Additionally, receiving non-crucial notifications is likely to cause desensitization in the perception of alarm signalling, defined as alarm fatigue [14,15]. This may lead to the missing of crucial information and suboptimal care for patients. To enhance scalability of eHealth programs and decrease the risk of alarm fatigue, incoming data should be automatically categorized and

assessed based on their urgence, minimizing the number of unnecessary alarms and non-actionable notifications by the eHealth team, with at least equivalence in quality of care compared to manual handling.

We aimed to identify factors for improvement in handling procedures for remote monitoring programs, and to translate these improvements into a generalizable strategy for optimizing eHealth protocols. Therefore, we studied all incoming data of the HartWacht hypertension program and compared two protocols in terms of workload by the "eHealth team" required for verification and handling of alarms and notifications.

METHODS

Study design and setting

We performed a retrospective analysis evaluating the Dutch HartWacht remote monitoring program for hypertension using real-world data.

HartWacht remote monitoring program

The Dutch HartWacht program, launched in 2016, is integrated in daily practice, fully reimbursed, and scaled up successfully [8]. Patients with hypertension are eligible for inclusion in the program at the discretion of the cardiologist. Patients are provided with a blood pressure monitoring device connected to a smartphone application and are instructed to measure blood pressure using a standardized protocol. Patients are requested to measure twice a day (morning and evening) in the first week of participation, followed by one measurement per week, and are instructed to measure after five minutes of rest in a seated position. Measurements are automatically registered in the smartphone app and simultaneously uploaded in the cloud-based personal electronic health record, for assessment by the eHealth team, consisting of trained eHealth nurses, who are supervised by a cardiologist with 24/7 availability. If deemed necessary, patients can add messages to their measurements. Notifications and corresponding follow-up actions re defined in protocols and designed to respond with lifestyle interventions or adaptations in therapeutic strategy based on structural, rather than incidental, exceeding of predefined thresholds.

We evaluated protocols for the handling of incoming data, that define which measurements lead to notifications for the HartWacht team. We compared two remote monitoring protocols (see supplements for protocol A and protocol B) that

differed in their set of rules for classifying the measurements that were performed by participating patients. We then measured the difference between the two protocols in workload (time spent on handling notifications) for the eHealth team and calculated potential associated cost savings.

Participating patients were referred to one of in total 12 outpatient cardiology clinics of Cardiology Centers of the Netherlands (CCN). Cardiologists consulted the patients about enrolment in the HartWacht program, which is reimbursed by Dutch insurance.

Study population and data collection

Patients diagnosed with hypertension participating in the Dutch HartWacht remote monitoring program in HartWacht were included in the analysis. All remote blood pressure measurements, notifications and related patient messages between January 2017 and April 2019 were extracted from the electronic health records. All measurements were reviewed by the eHealth team which acted according to protocol. These actions were used for analysis. All data used for this HartWacht-study were routinely documented in the EHR system. All data was analysed at CCN in accordance with its privacy statement [16].

Remote monitoring protocols

In protocol A, uploaded measurements are labelled green (within predefined thresholds), grey (within green thresholds with a message added by the patient), orange (slightly exceeding thresholds) or red (severely exceeding thresholds) (Figure 6.1). The gray, orange and red measurements result in a notification for the eHealth team and require personal response to the notification (See Appendix A).

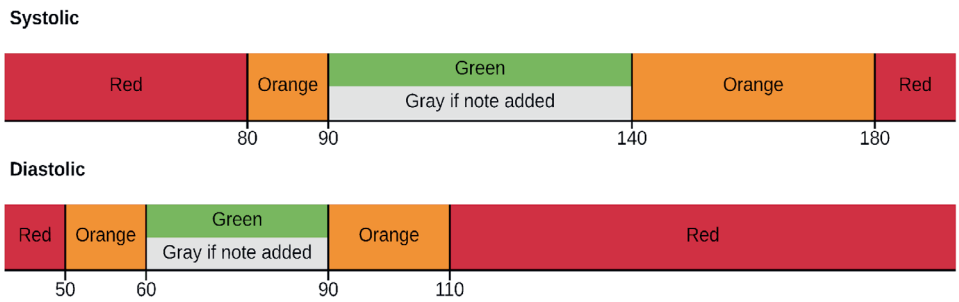


Figure 6.1: Standardized measurement classification for values of remote measured systolic and diastolic blood pressure for all HartWacht participants (mmHg).
Thresholds can be personalized at the discretion of the treating cardiologist.

For protocol B, we identified notifications that required follow-up that was defined as clinically irrelevant in protocol A, and designed it to omit these irrelevant actions. Based on literature, we defined three requirements for this alternative protocol to ensure equivalent quality of care, adherence and compliance:

1. Threshold values for blood pressure were defined by the guidelines for hypertension management and remain unchanged.
2. Patients are not limited in number and timing of the weekly blood pressure measurements, in order to maximize protocol adherence [16].
3. The amount of feedback that patients receive does not decrease compared to the historical protocol, to prevent a negative impact on compliance [17].

Considering these requirements, we redesigned the protocol to automatically discard all clinically irrelevant notifications and filter the messages based on predefined rules. The manual handling of orange notifications was replaced with automated grouping of those orange values in a weekly average. An orange notification was then only generated for consecutive weekly average values that were clinically relevant, leading to a lifestyle intervention or adaptation of drug therapy. Additionally, the possibility to add free-text messages was removed from the protocol and replaced by a predefined list of messages to add to their measurements which enables automatic classification of clinical relevance, so that relevant messages lead to direct alerts, while others are only presented at the weekly notifications, grouped together if applicable. No changes in the thresholds or for handling of red notifications were implemented, which are still generated on every individual measurement that exceeds the red threshold. Based on the observations, time per action was determined.

Definition and measurement of workload

We compared the two protocols on workload for the eHealth team. Time spent by this team per follow-up action while executing protocol A was observed and clocked (TB). The observations were used to classify and time all follow-up actions. Actions were classified as clinically relevant or irrelevant, where clinical relevance was defined as a handling, according to protocol, that affected therapeutic strategy (for example the handling of a red notification leading to a subsequent change in the patient's therapy). A clinical irrelevant action was defined as a handling according to protocol that did not affect therapeutic strategy, for example the handling of an incidental orange notification with no potential effect on the patient's therapy. The definitions for time per follow-up action and classification of clinical relevance as derived from protocol

A was then projected on the same dataset running through protocol B to compare the two. We analysed potential cost savings by comparing the total time spent in hours in the two protocols and multiply this with an hourly rate for a specialist nurse as generally used in the Netherlands (€47.60). We then calculated the average costs per patient per year for the handling of incoming data.

Data analysis

Data was analysed using IBM SPSS, version 23. A Shapiro Wilk test was used to test if continuous variables are normally distributed. Normally distributed variables are shown as the mean ± standard deviation. Continuous variables that were not normally distributed are shown as the median with the first and third quartile.

RESULTS

Database baseline characteristics

Between 1-1-2017 and 12-4-2019 a total of 169 patients (63 ± 10 years old, 43% female) performed at least one measurement in HartWacht (Table 6.1). The median participation time in the HartWacht program was eleven months. In the study period, patients executed a total of 10,255 remotely supervised blood pressure measurements.

Table 6.1: Baseline patient characteristics

Patient characteristics	N = 169
Female, n (%)	73 (43)
Age, y ± SD	63.2 ± 9.7
Participation in HartWacht, months (IQR)	11.0 (5.5, 17.0)
Office systolic blood pressure, mmHg ± SD	159 ± 21
Office diastolic blood pressure, mmHg ± SD	93 ± 13
Body mass index, mmHg ± SD	28 ± 4
Smoking, n (%)	76 (45)
Diabetes Mellitus, n (%)	18 (11)
Dyslipidemia, n (%)	38 (23)

Office blood pressure was defined as the last known measurement in an outpatient setting before baseline. Diabetes mellitus and dyslipidemia as recorded in patients' medical file.

Home measurements and incoming data

A total of 2,331 (22%) measurements led to a notification that was handled by the HartWacht team. These measurements contained a message from the patient and/or were outside of the thresholds (orange or red). From the 2,331 notifications, 848 (36%) were classified as clinically relevant. The notifications required a total handling time of 4,589 minutes (76.5 hours), of which 3,106 (68%) was spent on clinically relevant ones. Among the relevant notifications, 213 were red and 349 were orange. The irrelevant notifications consisted of 532 measurements that were performed within one week from the previous measurement, 808 incidental or first orange notifications and 143 second consecutive measurements that did not lead to a lifestyle intervention according to protocol (as the previous intervention was less than six months ago).

A total of 281 measurements contained a message that was added by the patient (among them 112 within green thresholds), of which 18 were considered clinically relevant. In these 18 messages patients mentioned for instance complaints like dizziness, palpitations, or chest pain. The other messages contained for instance reasons for not adhering to measurement frequency, changes in general physical condition or information about the setting of the measurement.

We used the same real-world HartWacht database of remote measurements to run through protocol B. This resulted in a total of 933 relevant notifications for the eHealth team, consisting of 231 direct notifications due to either BP values outside of red thresholds or a relevant text message, and 702 weekly average notifications. Following the revised notification criteria, measurements were grouped and notifications previously marked as irrelevant were considered in average values. Therefore, the number of relevant orange notifications increased from 349 to 434, whereas the number of red notifications remained the same. Because patient messages with the notifications were standardized, the time spent on reading decreased from 3 to 2 minutes per message. Handling all notifications and messages required a total of 3,160 minutes (52.7 hours), of which. Compared to protocol A, running protocol B on the real-world HartWacht data led to 60% less notifications, and 31% less time spent on handling those notifications (Figure 6.2).

The time spent in protocol A, 76.5 hours, corresponds with €3,640 total costs for handling of incoming measurements, while the total costs in protocol B are €2,507. On average this accounts for €23.50 and €16.18 per patient per year respectively. These costs don't include time spent on remote consultations with patients, lifestyle advice and intake and follow-up consultations.

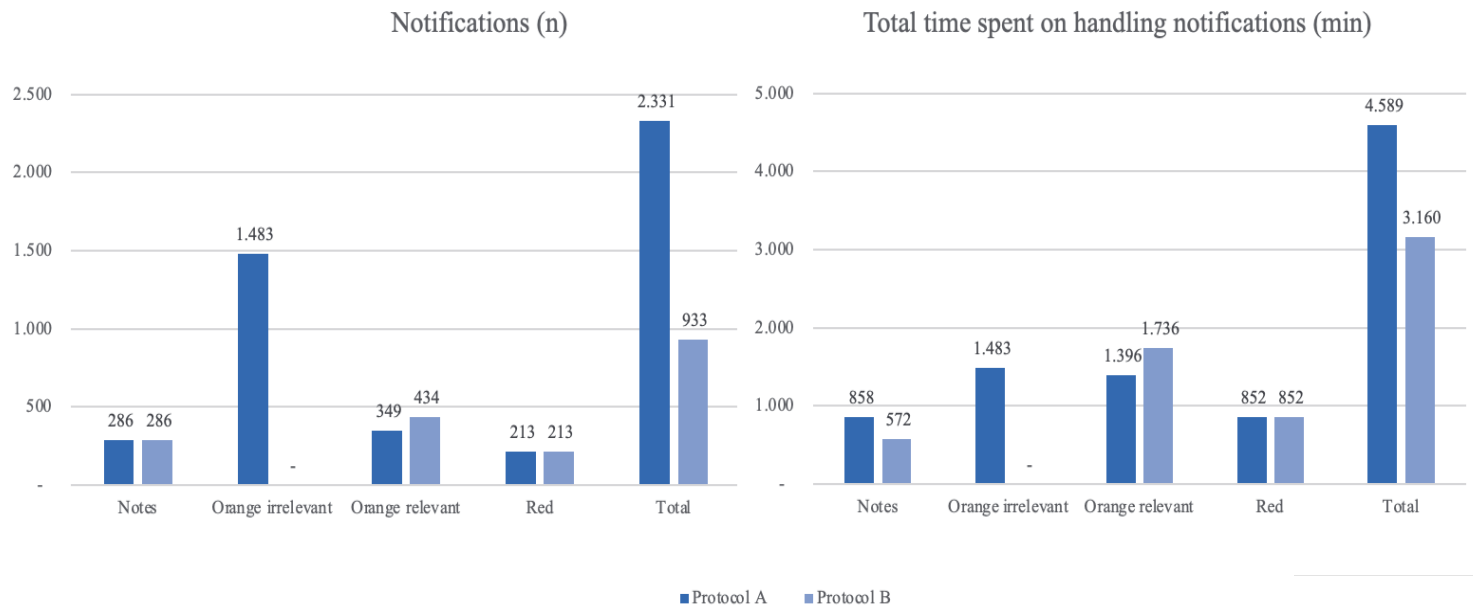


Figure 6.2: Comparison of number of notifications and workload between protocol A and B.

DISCUSSION

Key findings

By applying relatively easy automated processes to eHealth infrastructures, such as grouping measurements into average values and using pre-defined options for patients instead of free text, workload for eHealth teams can be considerably reduced while maintaining all notifications for the team that are clinically relevant. Simultaneously, eliminating notifications that we classify as clinically irrelevant reduces the risk of 'alarm fatigue' and thereby increases quality of care.

Discussion of key findings

eHealth programs can be effective in achieving clinical outcomes, such as blood pressure control for hypertensive patients [2–4,6,18]. However, one of the reasons that successful examples of large integrated infrastructures are scarce is that the increase in data coming from remote measurements is not handled efficiently and therefore hampers successful implementation and scalability. Additionally, receiving clinically irrelevant alarms or notifications can lead to alarm fatigue, as has been extensively described for clinical settings [19]. Alarm fatigue can cause apathy and desensitization of physicians and harm patient safety because it makes real events less likely to be acted on [19]. Therefore, healthcare providers raised concerns on the possible excessive number of readings, leading to reluctancy to further develop remote monitoring systems [20,21].

In our study, costs per patient per year for data handling seem limited, however timing of incoming notifications is irregular, and the follow-up actions are therefore inefficient. For remote monitoring programs with large numbers of connected patients a 31% decrease in workload has significant impact. The amount of €16 per patient per year for data handling, not including costs for intake and follow-up consultations and for instance lifestyle advice, as we observed in protocol B could be acceptable for large scale monitoring of patients with hypertension. In the Netherlands alone, when remote monitoring programs become increasingly efficient and cost-effective, they become accessible for a larger part of the 2.8 million patients currently diagnosed with hypertension [22].

The use of automated handling of notifications to decrease the chance of alarm fatigue has been proposed and implemented in for instance intensive care environments. As eHealth programs, such as remote monitoring programs for the management of hypertension, are relatively new and characterized by a large amount of incoming data,

optimization of protocols for automated handling of notifications is of great potential value. For instance, automated transmission of home BPs into a usable, analysable data set, seamless entering of remotely measured values in the same program where the clinical algorithm operates and integration with the electronic medical record are essential for successful upscaling [23]. In our study we observed that a limited number of patients (169) leads to more than 10,000 datapoints, so changes in automatization of protocols can have considerable impact. The lack of such protocols is one of the reasons large scale monitoring programs, with self-measurement by patients and remote personalized feedback, have not yet been implemented, despite evidence on its contribution to blood pressure control [7]. Research on this topic is crucial to reduce workload and associated costs without harming effectiveness.

In previous research, the development of algorithms for remote blood pressure monitoring has been described [23]. Although focussing on medication titration rather than long term monitoring as we did in our paper, grouping measurements to averages similarly demonstrated to be essential for scalability. Our study adds knowledge by using real-world data from an integrated and reimbursed remote monitoring program to draw generalizable conclusions for scalable and high-quality eHealth programs.

We identified three generalizable critical factors for eHealth to live up to its promise and bring us closer to accessible, affordable and scalable healthcare. First, an eHealth protocol should provide notifications based on average values instead of incidental measurements. This prevents prompt and unnecessary action, but simultaneously keeps actual anomalies from remaining unnoticed. In the HartWacht program we found that averaging single measurements into a weekly average, leads to a decrease from 2,331 incidental notifications, largely clinically irrelevant, to 933 relevant notifications that are largely plannable (weekly). In the present analysis this led to a 31% workload reduction and decreases the risk of alarm fatigue because of avoidance of non-crucial notifications. Second, an eHealth protocol should provide pre-defined options for patients to add messages which are classified according to their clinical relevance, thereby decreasing ad-hoc time spent by the eHealth team reading irrelevant messages. For instance, in the HartWacht program we observed that when given a free text message option, only 6% of added messages were of clinical relevance, all other messages did not require (immediate) attention from the eHealth team. Finally, an eHealth protocol should allow for flexibility for patients choosing their moment to add measurement and to measure more than prescribed. For instance, the HartWacht protocol was designed for weekly measurements. However, in practice, patients chose different days to measure or did so more frequently. As the protocol was designed for

the eHealth team to check all non-prescribed measurements, all these measurements were checked instantly. Using weekly averages, workload is substantially decreased with at least equivalent quality of care.

Strengths and limitations

For the comparison between the two protocols, we used real world data from a remote monitoring program that is integrated in outpatient cardiology clinics. It represents the reality of daily practice, thereby increasing the generalizability of the results. We used the same database of measurements for both protocols rather to increase the comparability of the workload in both situations. However, of the two protocols only A has been implemented in the HartWacht remote monitoring program. For future research, we recommend applying protocol B as well to evaluate possible challenges in its implementation.

Conclusion

eHealth programs for chronic diseases lead to a large amount of additional data compared to traditional healthcare. Such programs can only be cost-effective if the majority of data is automatically interpreted and handled. A flexible set-up of the eHealth protocol, based on average instead of single measurements, and standardizing personal input are key success factors for a scalable and cost-effective infrastructure with at least equivalent quality of care.

Acknowledgement

We are most thankful for the contributions of participants and staff.

Statement on conflicts of interest

Authors declare no conflicts of interest.

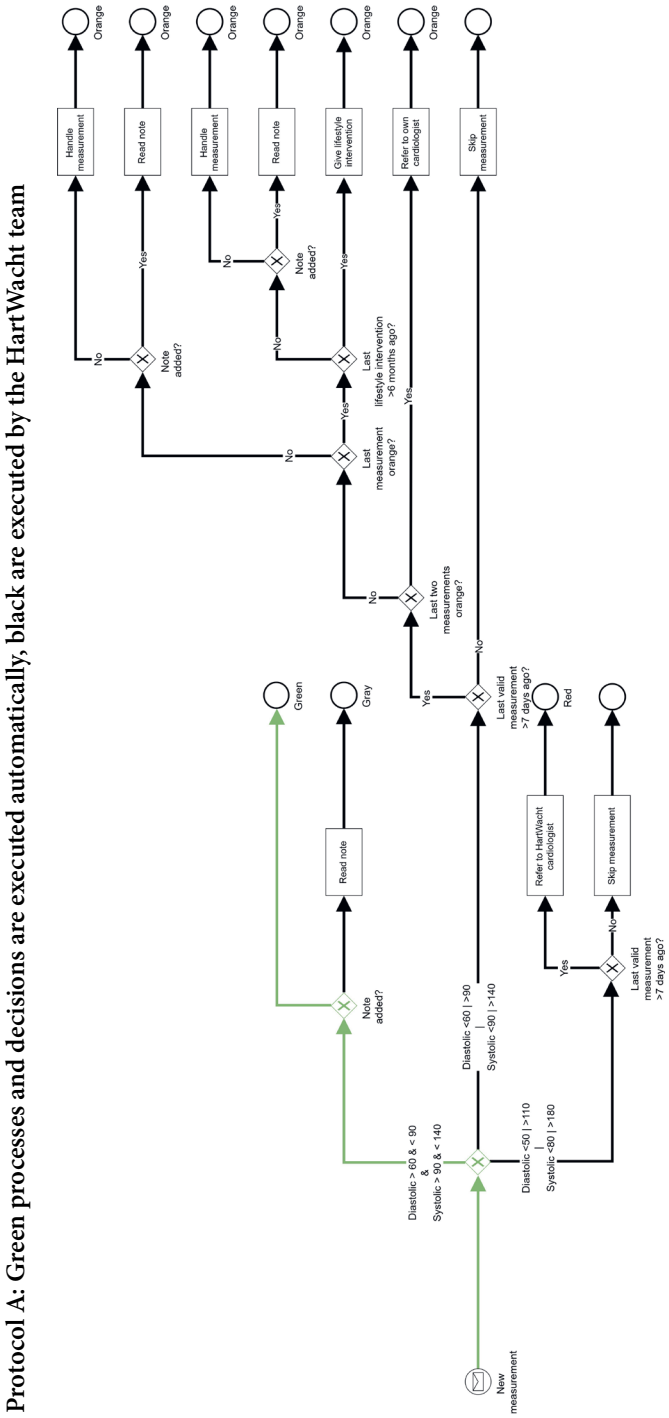
REFERENCES

1. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe: epidemiological update. *Eur Heart J* 2013; 34: 3028–3034.
2. Copetti A, Loques O, Leite JCB, et al. Intelligent context-aware monitoring of hypertensive patients. In: *Proceedings of the 3d International ICST Conference on Pervasive Computing Technologies for Healthcare*. ICST. Epub ahead of print 2009. DOI: 10.4108/ICST.PERVASIVEHEALTH2009.6058.

3. Mohammadi R, Ayatolahi Tafti M, Hoveidamanesh S, et al. Reflection on Mobile Applications for Blood Pressure Management: A Systematic Review on Potential Effects and Initiatives. *Stud Health Technol Inform* 2018; 247: 306–310.
4. Cappuccio FP, Kerry SM, Forbes L, et al. Blood pressure control by home monitoring: meta-analysis of randomised trials. *BMJ* 2004; 329: 145.
5. Stoddart A, Hanley J, Wild S, et al. Telemonitoring-based service redesign for the management of uncontrolled hypertension (HITS): cost and cost-effectiveness analysis of a randomised controlled trial. *BMJ Open*; 3. Epub ahead of print May 2013. DOI: 10.1136/bmjopen-2013-002681.
6. Tucker KL, Earle K, Bray EP, et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. *PLOS Med* 2017; 14: e1002389.
7. Blok S, van der Linden EL, Somsen GA, et al. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; 2047487320957170.
8. Peeters JM, Krijgsman JW, Brabers AE, et al. Use and Uptake of eHealth in General Practice: A Cross-Sectional Survey and Focus Group Study Among Health Care Users and General Practitioners. *JMIR Med Informatics* 2016; 4: e11.
9. ten Klooster I, Wentzel J, Sieverink F, et al. Personas for Better Targeted eHealth Technologies: User-Centered Design Approach. *JMIR Hum Factors* 2022; 9: e24172.
10. Arts DL, Abu-Hanna A, Medlock SK, et al. Effectiveness and usage of a decision support system to improve stroke prevention in general practice: A cluster randomized controlled trial. *PLoS One* 2017; 12: e0170974.
11. Selder JL, Breukel L, Blok S, et al. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.
12. Wierda E, Blok S, Somsen GA, et al. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of Hartwacht as a learning case. *BMJ Innov* 2020; 6: 170–176.
13. Kolk MZH, Blok S, De Wildt MCC, et al. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal*. Epub ahead of print 9 March 2021. DOI: 10.1093/ehjdh/ztab030.
14. Chopra V, McMahon LF. Redesigning Hospital Alarms for Patient Safety. *JAMA* 2014; 311: 1199.
15. Oliveira AEC de, Machado AB, Santos ED dos, et al. Alarm fatigue and the implications for patient safety. *Rev Bras Enferm* 2018; 71: 3035–3040.
16. Kronish IM, Kent S, Moise N, et al. Barriers to conducting ambulatory and home blood pressure monitoring during hypertension screening in the United States. *J Am Soc Hypertens* 2017; 11: 573–580.
17. Wang JG, Bunyi ML, Chia YC, et al. Insights on home blood pressure monitoring in Asia: Expert perspectives from 10 countries/regions. *J Clin Hypertens* 2021; 23: 3–11.
18. McKinstry B, Hanley J, Wild S, et al. Telemonitoring based service redesign for the management of uncontrolled hypertension: Multicentre randomised controlled trial. *BMJ* 2013; 346: 1–18.
19. Fernandes C, Miles S, Lucena CJP. Detecting false alarms by analyzing alarm-context information: Algorithm development and validation. *JMIR Med Informatics*; 8. Epub ahead of print 2020. DOI: 10.2196/15407.

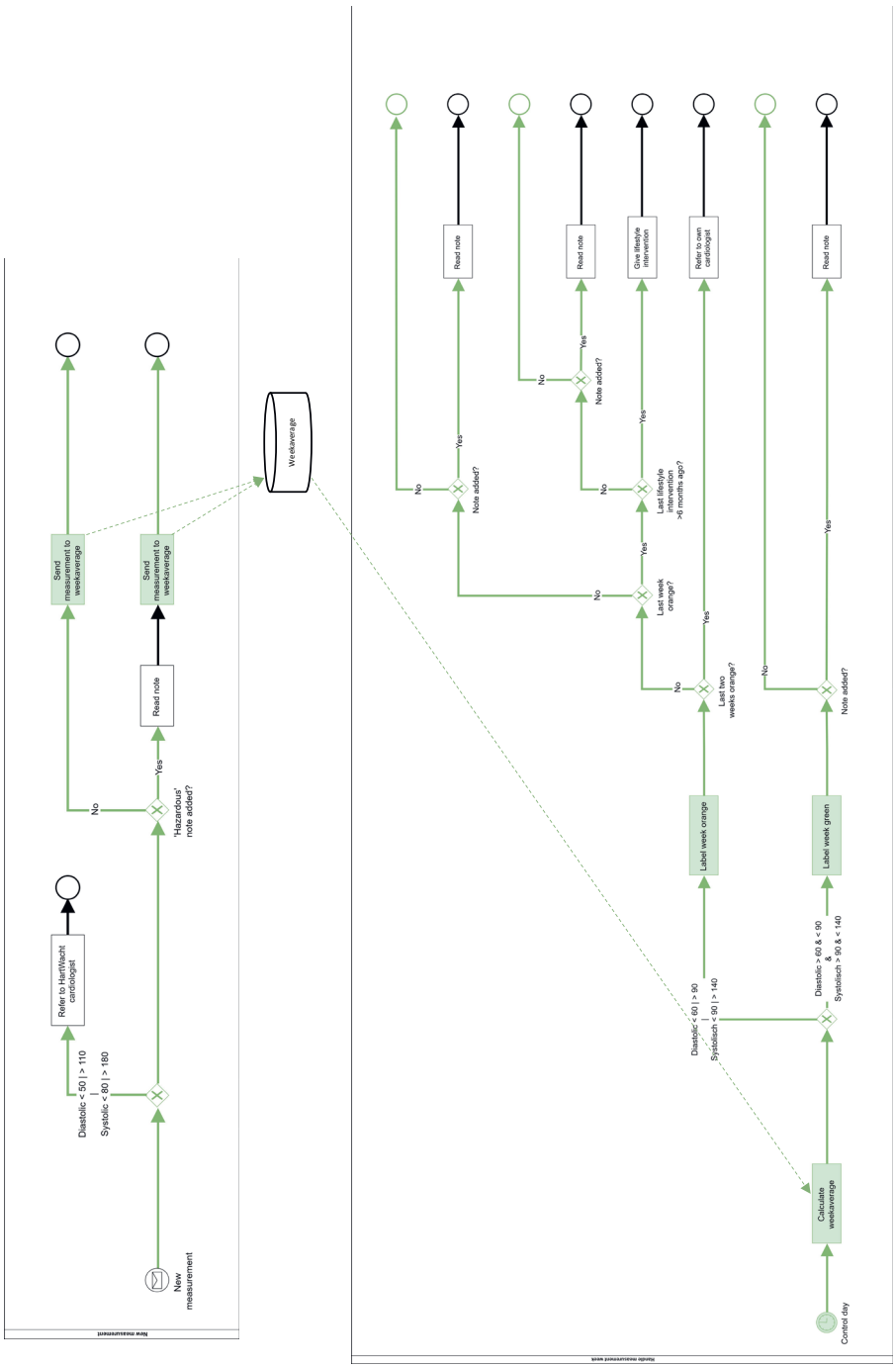
20. Jones MI, Greenfield SM, Bray EP, et al. Patient self-monitoring of blood pressure and self-titration of medication in primary care: The TASMINH2 trial qualitative study of health professionals' experiences. *Br J Gen Pract* 2013; 63: 378–385.
21. Rodriguez S, Hwang K, Wang J. Connecting home-based self-monitoring of blood pressure data into electronic health records for hypertension care: A qualitative inquiry with primary care providers. *JMIR Form Res*; 3. Epub ahead of print 2019. DOI: 10.2196/10388.
22. RIVM. Bloeddruk, https://www.vzinfo.nl/bloeddruk (2022, accessed 14 May 2022).
23. Fisher NDL, Fera LE, Dunning JR, et al. Development of an entirely remote, non-physician led hypertension management program. *Clin Cardiol* 2019; 42: 285–291.

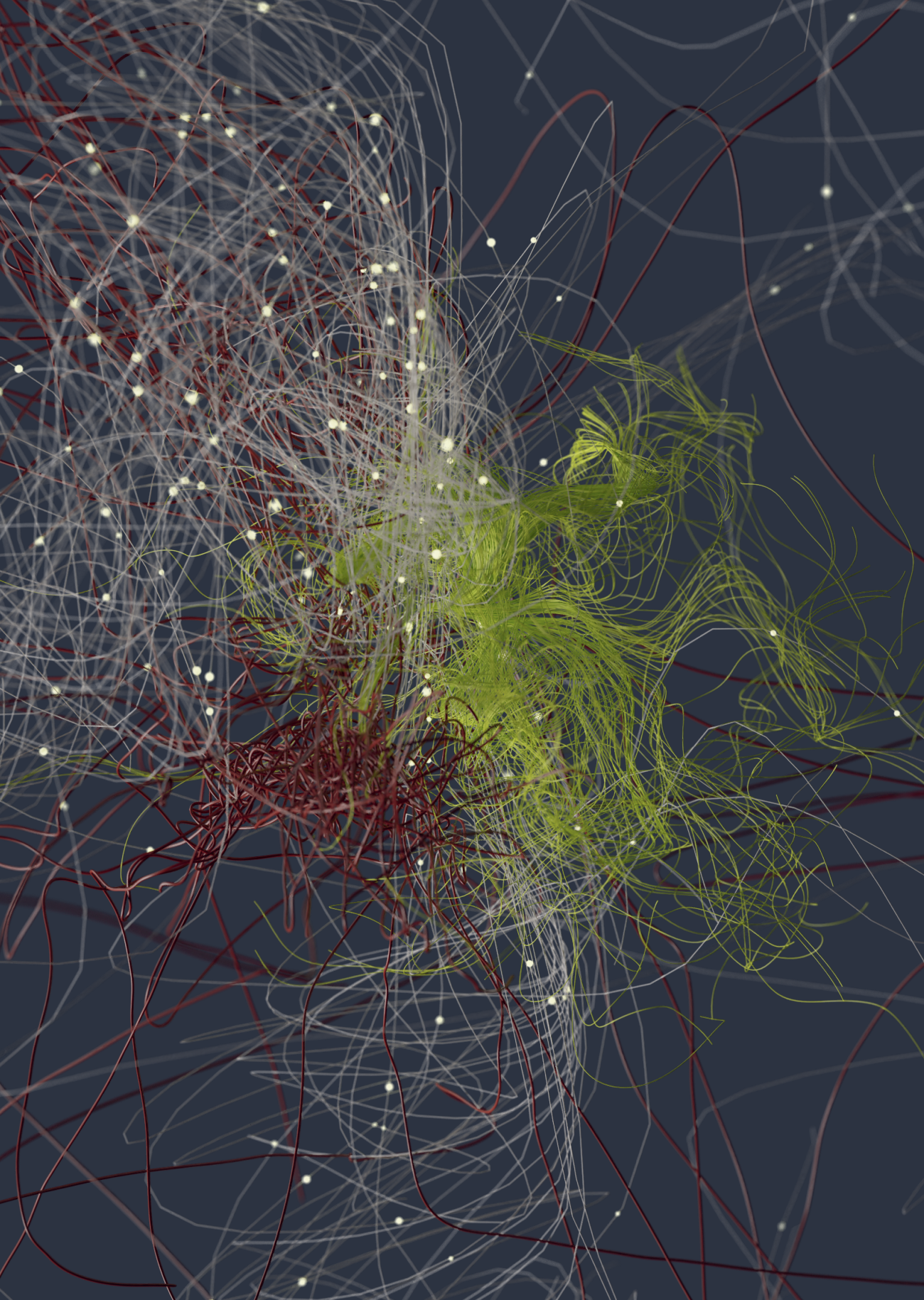
SUPPLEMENTARY MATERIALS



Protocol A: Green processes and decisions are executed automatically, black are executed by the HartWacht team

Protocol B: Green processes and decisions are executed automatically, black are executed by the HartWacht team





Chapter 7

Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: Evaluation of the Dutch HartWacht-telemonitoring program

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ABSTRACT

Background: There is limited quantitative evidence on the effect of symptom-driven telemonitoring for cardiac arrhythmias on patient-reported outcomes. We evaluated the effect of a symptom-driven remote arrhythmia monitoring program on the patient-reported health-related quality of life (HRQoL), sense of safety, physical limitations and self-management.

Methods: This was an observational retrospective longitudinal study of the symptom-driven HartWacht-telemonitoring program using a remote single-lead electrocardiogram (ECG) monitoring system. Real-world patient data from participants who were enrolled in the telemonitoring program for (suspected) symptomatic atrial fibrillation (AF) between July 2017 and September 2019 were evaluated. Primary outcomes were the patient-reported generic HRQoL, disease-specific HRQoL, sense of safety, physical limitations and self-management at date of enrolment, three months and six months of follow-up. Outcomes were compared to a historical control group consisting of AF patients receiving standard care.

Results: A total of 109 participants in the HartWacht-program (59 men (54%); mean age 61 ± 11 years; 72% diagnosed AF) were included in complete case analysis. There was no significant change in HRQoL and sense of safety during follow-up. A significant improvement in the perceived physical limitations was observed. The level of self-management declined significantly during follow-up. Comparisons to the historic control group (n=83) showed no difference between the patient-reported disease-specific HRQoL, sense of safety and physical limitations at six months follow-up.

Conclusion: Symptom-driven remote arrhythmia monitoring for AF does not seem to affect HRQoL and sense of safety, whereas the perceived physical limitations tend to improve. Patient-reported self-management declined during the first six months of participation.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated prevalence of 260,000 patients in the Netherlands alone (prevalence of 1-4%) [1]. Since AF predominantly manifests in older adults, its incidence has increased with advancing ages over the past decades and will continue to rise in the future [2–5]. Prior research has demonstrated an adverse effect of AF on health-related quality of life (HRQoL) [6]. Especially the presence of arrhythmia-related symptoms, symptom-related anxiety, symptom frequency and symptom severity have been associated with a decline in HRQoL [7]. Furthermore, patients with AF generally report low levels of self-management and reluctance towards physical activity [8,9]. Over the past decade there has been an increase in the implementation of eHealth strategies such as telemonitoring, which aim to improve safety and quality of care, enhance efficiency and support communication between healthcare providers and patients [9–11]. Nevertheless, eHealth can only live up to its promise if HRQoL is preserved and remains equivalent to usual care. Evidence on the effect of symptom-driven remote arrhythmia monitoring on patient-reported outcomes such as HRQoL, physical limitations, self-management and sense of safety is however limited. A feasibility study evaluating symptom-driven telemonitoring for patients (n = 12) with arrhythmia-related symptoms demonstrated an improvement in the HRQoL during six months of participation, but this lacked statistical significance [12]. Therefore, we performed an observational retrospective longitudinal study using real-world data to evaluate the effect of symptom-driven remote arrhythmia monitoring for AF on patient-reported health-related quality of life, sense of safety, physical limitations and self-management.

METHODS

Study design and setting

This was a retrospective observational longitudinal study design evaluating the Dutch HartWacht-telemonitoring program for (suspected) AF using real-world data. Eligible patients were referred to one of in total 12 outpatient cardiology clinics of Cardiology Centers of the Netherlands (CCN). Cardiologists consulted the patients about enrollment in the HartWacht program, which was reimbursed by most Dutch insurance companies.

Study population and patient selection

The study population consisted of patients who were enrolled in the HartWacht-telemonitoring program between July 2017 and September 2019. Participants needed to be older than 18 years and either diagnosed with (a) symptomatic AF or (b) having complaints of palpitations of unknown origin suspected of AF. Exclusion criteria for the HartWacht-telemonitoring program were unwillingness to participate or to follow the online training program, having tremors or an impaired cognition as assessed by the cardiologist. Out of pocket payment was allowed for patients without the appropriate health insurance. Participants who did not own a smart device were not able to participate. Enrollment in the HartWacht-telemonitoring program was at the cardiologists' discretion based on individual patient circumstance and the patient's willingness to participate. All patients who enrolled in the HartWacht-telemonitoring program who were diagnosed with AF were evaluated and treated according to the European Society of Cardiology (ESC) Guidelines on the Management of Atrial Fibrillation [13]. For explorative reasons, outcomes were compared to a historic control group consisting of patients who were diagnosed with AF and received standard care instead of HartWacht-telemonitoring at CCN. Patients in the control group visited the CCN in the same period as the HartWacht-participants.

HartWacht-telemonitoring for atrial fibrillation

Participants in the HartWacht-telemonitoring program received the KardiaMobile (KM, AliveCor, Inc. Mountain View, CA United States) remote ECG monitoring device which had to be connected to the KM Application on a participant-owned smart device such as a smartphone or tablet. Participants were instructed to record a 30-seconds single lead electrocardiogram (ECG) when they experienced palpitations or other arrhythmia-related symptoms (e.g. dizziness, shortness of breath, fainting, syncope etc.) in an ambulant setting. ECG recordings were instantly assessed by the KM ECG analysis algorithm which classified the ECG as either sinus rhythm or potentially abnormal. The outcome of the classification was directly available on the participant's smart device. All ECGs were subsequently interpreted by a dedicated remote healthcare team consisting of a supervising cardiologist and specialized nurses (*HartWacht-team*). According to the HartWacht-protocol, personalized feedback to the participants was provided if there were implications for the patient based on the recording (e.g. to arrange a consultation at the outpatient clinic, referral to the emergency department or for reassurance). If the ECG recordings were not eligible for assessment due to artefacts, participants were asked to make a new recording. There

were no restrictions on the number of ECGs participants could record. To ensure the quality of the ECG recordings, participants were provided with an online instruction video, complemented with a personal onboarding consultation if needed. Participants were allowed to stop their participation at any time during the program.

Measurements

The primary outcomes in this study were the health-related quality of life, sense of safety, physical limitations, and self-management measured using self-administered questionnaires at time of enrollment in the HartWacht-program, three months and six months of follow-up. Participants received these questionnaires via email and were able to fill out the questionnaires in a secure online environment until four weeks after they had received it. A reminder was sent to participants who did not fill out the questionnaires after two weeks. The patient-reported outcomes were routinely sent, collected and documented in the electronic health record (EHR). The three questionnaires were the Care Related Quality of Life for Chronic Heart Failure (CaReQoL CHF), the EuroQoL 5-Dimensions 5-Levels (EQ5D-5L) and the Patient Activation Measure (PAM)-13-NL [14–16]. The historic control group only received the CaReQoL CHF questionnaire. The CaReQoL CHF questionnaire consists of 20 items scored on a five-point Likert-scale, categorized into three domains: sense of safety, physical limitations and social-emotional problems (scores ranging from 1.00 (worst score) till 5.00 (best score)). Secondly, the EQ5D-5L questionnaire is a generic, preference-based questionnaire as a measure for the HRQoL. The EQ5D-5L questionnaire consists of a descriptive system which comprises five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The EQ5D-5L utility index for HRQoL ranges between -0.590 (worst score) and 1.000 (best score). Each of the five domains is scored between 1.00 (no problems) and 5.00 (severe problems). Third, the PAM-13-NL questionnaire was used to assess the patients' knowledge of and confidence in their self-management. The PAM-13-NL consists of 13 items scored on a four-point Likert scale. Raw PAM-13 scores were subdivided into different levels of self-management (level 1-4): start of role taking (level 1); gaining knowledge and confidence (level 2); taking action (level 3) and sustaining behaviour change (level 4). All data used for this HartWacht-study, including the abovementioned questionnaires, were routinely documented in the EHR system. All data was analysed at CCN in accordance with its privacy statement [17].

Statistical analysis

All primary outcomes were continuous variables and presented by its median, mean, interquartile range (IQR) and standard deviation (SD). Categorical sociodemographic and clinical variables were presented as frequencies (percentages). The Kolmogorov-Smirnov test was used to assess whether there was a normal distribution. The nonparametric Friedman two-way analysis of variances was used to compare the patient-reported outcomes at baseline and during follow-up assuming there was a non-normal distribution. Categorical sociodemographic and clinical variables were compared between participants in the HartWacht-telemonitoring program and patients receiving standard outpatient care using the Chi-square test when appropriate, otherwise using Fisher's exact test. Means were compared using independent T-tests and tested for equality of variances using Levene's Test, or using the nonparametric Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant. Non-responders were defined as the participants who did not respond to one or more questionnaires at three months and/or six months follow-up. Separate analysis regarding the non-responders was performed to gain insight in the characteristics of participants from whom follow-up was lost. All statistical analyses were performed using SPSS Statistics IBM version 24.

RESULTS

In total, 256 participants in the HartWacht-telemonitoring programme were eligible for the study. Of these 256 participants, 147 participants (57%) did not respond to the questionnaires at 3 months and/or 6 months of follow-up. A total of 109 participants (59 men (54%); mean age 61 ± 11 years) were included in complete case analysis and described in Table 7.1. There were no significant differences in sociodemographic and clinical characteristics between the non-responders and the responders, whereas sense of safety and self-management at baseline were significantly lower among non-responders compared to responders (Supplementary Materials, Table S7.1). The median monthly number of recordings was 2.4 (IQR 0.85-5.94) among responders to the questionnaires, compared to 1.8 (0.40-4.90) recordings among non-responders ($p = 0.153$). In total, 79 (72%) of responders were diagnosed with AF at time of enrolment in the HartWacht programme, which was lower among non-responders 75 (51%). Paroxysmal AF was the most common diagnosis in both the HartWacht group (44%) and control group (42%) (Supplementary Materials, Table S7.2).

Table 7.1: Sociodemographic and clinical characteristics of patients participating in the HartWacht-telemonitoring program (n = 109)

	HartWacht-telemonitoring (n = 109)
Sociodemographic variables	
Age, years	61.3 (10.9)
Age ≥ 70 years old, yes (n, %)	20 (18)
Gender, male (n, %)	59 (54)
Clinical variables	
Number of medications	3.8 (3.0)
Body mass index	25.3 (4.0)
General morbidity, yes (n, %)	
Atrial fibrillation	78 (72)
Psychiatric disorder(s)	10 (9)
Cerebral vascular accident(s)	1 (1)
Chronic heart failure	3 (3)
Cardiovascular risk factors (n, %)	
Hypertension	45 (41)
Hypercholesterolemia	23 (21)
Diabetes mellitus	8 (7)

Data presented as mean (SD) unless otherwise indicated. SD = standard deviation.

Patient-reported outcomes

The primary outcomes of the EQ5D-5L and CaReQoL CHF questionnaires at baseline and during follow-up are displayed in Table 7.2. Longitudinal analysis showed no significant change in the EQ5D-5L utility index for HRQoL ($p = 0.43$). A positive trend in the overall HRQoL as measured with the disease-specific CaReQoL CHF questionnaire was observed, but this lacked statistical significance ($p = 0.06$). There was no significant change in the sense of safety from baseline until 6 months of follow-up ($p = 0.55$). The patient-reported physical limitations ($p = 0.002$) and EQ5D-5L domain usual activities ($p = 0.01$) both showed a significant improvement during follow-up. No significant change was seen in the EQ5D-5L domains mobility, self-care, pain/discomfort, and anxiety/depression during follow-up. The level of patient-reported self-management significantly declined during follow-up ($p < 0.001$), where 92.6% of participants were at level 3 (taking action) or 4 (sustaining behaviour change) at baseline, 74.3% of participants reported these levels of self-management after 6 months of follow-up (Figure 7.1). Comparisons of the CaReQoL CHF outcomes HRQoL, physical limitations and sense of safety between the historical control group (57 men (69%), mean age 69.3 ± 7.9 years) and the HartWacht group showed equivalence at 6 months of follow-up (Table 7.3). No significant changes in the HRQoL ($p = 0.14$),

Table 7.2: Patient-reported outcomes in the HartWacht-telemonitoring program at baseline and during follow-up (n = 109)

	Baseline		3 months		6 months		
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	p-value[a] for trend
CaReQoL HRQoL	4.04 (0.63)	4.16 [3.57-4.57]	4.16 (0.60)	4.28 [3.67-4.66]	4.18 (0.65)	4.35 [3.75-4.76]	0.06
Social-emotional problems	4.06 (0.72)	4.19 [3.44-4.67]	4.38 (0.66)	4.67 [3.89-5.00]	4.39 (0.68)	4.67 [4.00-4.89]	< 0.001
Physical limitations	3.92 (0.81)	4.14 [3.43-4.57]	4.08 (0.72)	4.29 [3.57-4.57]	4.14 (0.74)	4.29 [3.71-4.71]	0.002
Sense of safety	4.25 (0.71)	4.50 [3.75-4.75]	4.17 (0.88)	4.25 [3.75-5.00]	4.15 (0.91)	4.25 [3.67-5.00]	0.55
EQ5D-5L utility index	0.852 (0.13)	0.845 [0.765-1.000]	0.866 (0.13)	0.874 [0.765-1.000]	0.867 (0.14)	0.874 [0.765-1.000]	0.43
Mobility	1.25 (0.61)	1.00 [1.00-1.00]	1.29 (0.61)	1.00 [1.00-1.00]	1.33 (0.68)	1.00 [1.00-1.00]	0.36
Self-care	1.02 (0.13)	1.00 [1.00-1.00]	1.06 (0.23)	1.00 [1.00-1.00]	1.07 (0.30)	1.00 [1.00-1.00]	0.07
Usual activity	1.51 (0.81)	1.00 [1.00-2.00]	1.38 (0.66)	1.00 [1.00-2.00]	1.40 (0.67)	1.00 [1.00-2.00]	0.01
Pain/discomfort	1.68 (0.69)	2.00 [1.00-2.00]	1.61 (0.73)	1.00 [1.00-2.00]	1.55 (0.71)	1.00 [1.00-2.00]	0.10
Anxiety/ depression	1.47 (0.68)	1.00 [1.00-2.00]	1.46 (0.67)	1.00 [1.00-2.00]	1.45 (0.63)	1.00 [1.00-2.00]	0.92

Data presented as mean (SD) and median [IQR]. HRQoL = Health-Related Quality of Life, CaReQoL = Care Related Quality of Life for Chronic Heart Failure, EQ5D-5L = EuroQoL 5-dimension 5-level, SD = standard error, IQR = interquartile range. [a] Friedman test for multiple related samples.

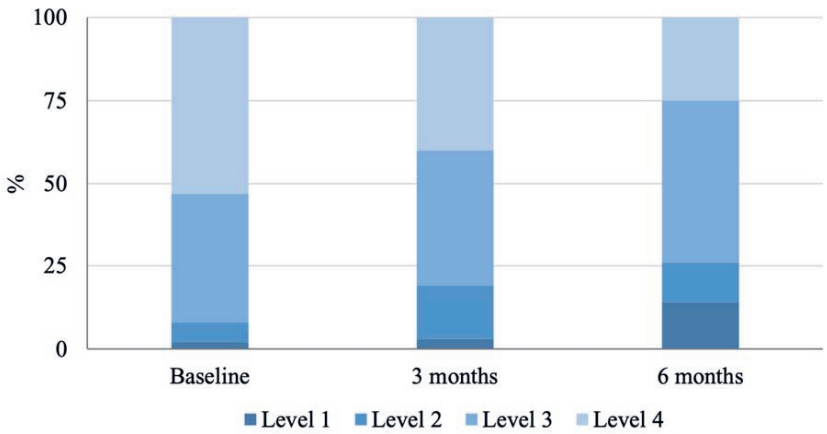


Figure 7.1: Percentage of participants in the HartWacht-telemoni- toring programme (n = 109) per level of self-management measured using the Patient Activation Measure (PAM)-13-NL questionnaire at baseline and during follow-up.
The four levels of self-management, ranging from a low (level 1) to a high (level 4) level of self- management.

physical limitations (p = 0.45), and sense of safety (p = 0.60) were seen in the historic control group during follow-up (Table 7.4). The domain social-emotional problems improved during 6 months of follow-up both in the historic control group (p < 0.001) and the HartWacht group (p < 0.001).

Table 7.3: Comparison of a historical control group receiving standard care (n = 83) and HartWacht-telemonitoring (n = 109)

	Standard care (n = 83)	HartWacht-telemonitoring (n = 109)	p-value[a]
CaReQoL HRQoL			
Baseline	4.15 (0.56)	4.04 (0.63)	0.28
3 months	4.24 (0.59)	4.16 (0.60)	0.35
6 months	4.19 (0.55)	4.18 (0.65)	0.73
Social-emotional problems			
Baseline	4.29 (0.68)	4.06 (0.72)	0.02
3 months	4.53 (0.59)	4.38 (0.66)	0.05
6 months	4.47 (0.60)	4.39 (0.68)	0.34
Physical limitations			
Baseline	3.94 (0.86)	3.92 (0.81)	0.81
3 months	3.99 (0.84)	4.08 (0.72)	0.70
6 months	4.01 (0.83)	4.14 (0.74)	0.34
Sense of safety			
Baseline	4.22 (0.74)	4.25 (0.71)	0.82
3 months	4.18 (0.86)	4.17 (0.88)	0.99
6 months	4.10 (0.90)	4.15 (0.91)	0.65

[a] Independent-Samples Mann-Whitney U-test.

Table 7.4: CaReQoL HRQOL outcomes in the historical control group receiving standard care (n = 83) at baseline and during follow-up

	Baseline		3 months		6 months		
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	p-value[a] for trend
CaReQoL HRQoL	4.15 (0.56)	4.23 [3.78-4.58]	4.24 (0.59)	4.31 [3.91-4.70]	4.19 (0.55)	4.22 [3.90-4.65]	0.14
Social-emotional problems	4.29 (0.68)	4.56 [4.00-4.78]	4.53 (0.59)	4.78 [4.22-5.00]	4.47 (0.60)	4.67 [4.11-5.00]	< 0.001
Physical limitations	3.94 (0.86)	4.14 [3.43-4.57]	3.99 (0.84)	4.14 [3.43-4.71]	4.01 (0.83)	4.14 [3.40-4.71]	0.45
Sense of safety	4.22 (0.74)	4.33 [3.75-5.00]	4.18 (0.86)	4.33 [3.75-5.00]	4.10 (0.90)	4.25 [3.50-5.00]	0.60

[a] Friedman test for multiple related samples.

DISCUSSION

The aim of this retrospective observational longitudinal study using real-world data was to evaluate the effect of participation in the symptom-driven HartWacht-telemonitoring program for AF on the self-reported health-related quality of life (HRQoL) and the perceived sense of safety, physical limitations and self-management. Our results demonstrated (1) no significant change over time in the patient-reported HRQoL and perceived sense of safety, (2) a significant improvement in the patient-reported physical limitations and (3) a decline in the patient-reported self-management during six months follow-up. HRQoL, physical limitations and sense of safety in the HartWacht group showed equivalence to usual care.

Effect on health-related quality of life, sense of safety and physical limitations

The findings from our study demonstrated no significant change in HRQoL during follow-up in the HartWacht group and the historical control group, which is in line with the results from a randomized controlled trial (iHEART) that compared smartphone-based ECG monitoring using a KM device and behavioural text messaging to usual care. Similar to our study, the iHEART trial found equivalence between the intervention and usual care group on the EQ5D-5L utility index at 6 months follow-up [18]. In contrast to the iHEART trial which has evaluated a dual telemonitoring program using both ECG recordings and motivational text messaging, this HartWacht-study was primarily focussed on remote ECG monitoring. This has granted us the opportunity to solely reflect on the effect of an ECG remote monitoring program on HRQoL in everyday practice. Second, our hypothesis that the sense of safety of patients participating in the HartWacht-telemonitoring program is equivalent to those receiving usual care, was confirmed [19,20]. We expect the experienced sense of safety to potentially be higher than usual care if the direct and personalized feedback loop to participants following a recording would be consistently executed without exception, which has not been the case in the HartWacht-telemonitoring program. There were in fact situations possible in which recordings were categorized as possible AF by the algorithm but were not followed by a consultation with the HartWacht-team. There may be two explanations for this discrepancy. First, considering that the algorithm has a specificity of 0.95 for AF, there may have been situations where the HartWacht-team has overruled false positive assessments of the algorithm [21]. Second, recordings interpreted as AF were only followed by a consultation if the recording would have direct implications for the patient, for instance when it led to a new diagnosis or changes in medication. This occasional absence of an immediate and personalized feedback loop to the participants

following the recording of an ECG could have affected the perceived sense of safety [22,23]. Further, a prerequisite for participants to gain confidence in using a telemonitoring device is the practicality and simplicity of the device, the participant's experience with new technology, and the presence of training or assistance [24,25]. Despite the fact that new participants were instructed either by a video or a personal intake consultation by telephone, participants were presumably following a learning curve in mastering the device and familiarizing themselves with the HartWacht-program. However, due to potential advantages of eHealth regarding its cost-effectiveness and scalability compared to usual care, the absence of an adverse effect of the HartWacht-program on sense of safety further advocates the implementation of such programs [26]. Lastly, paroxysmal and symptomatic AF are associated with reduced physical activity due to the fear of provoking symptoms [8,27,28]. In this HartWacht-study, however, participants reported an improvement in perceived physical limitations and usual activities during follow-up. Similarly, in the iHEART randomized controlled trial a significant increase in the physical component summary of the Short-Form Health Survey (SF-36) was observed. Hence, from this we infer that symptom-driven remote arrhythmia monitoring could encourage patients to become more physically active [18,29].

Effect on self-management

A decline in the level of self-management has been associated with more primary care consultations, visits to the emergency department and hospitalizations, whereas high levels of self-management are associated with a healthy lifestyle, undertaking preventive measures, pro-active behaviour in the patient-doctor interaction and health literacy [30–33]. This study has shown that while approximately 91% of the patients were at higher levels of self-management at baseline, only 75% of patients reported these levels of self-management after six months of follow-up. This is the first study to evaluate self-management levels using symptom-driven remote arrhythmia monitoring, hence it is uncertain whether the PAM-13-NL questionnaire is an appropriate measure for self-management in this population. Additionally, the use of telemonitoring tends to negatively affect self-management if patients have questions or concerns that remain unanswered [34]. A previous RCT evaluating the effect of a mobile application for AF aimed to educate and increase patient-involvement illustrated a significant improvement in the patients' knowledge and drug adherence compared to standard care [35]. Hypothetically, the incorporation of patient education in a telemonitoring program could aid in sustaining, or even improving patient-reported self-management.

Strengths and limitations

The use of real-world data has granted us the opportunity to reflect on the current, every-day, real-world setting of the reimbursed HartWacht-telemonitoring program producing real-world evidence. Also, this is the first study to evaluate patient-reported self-management and sense of safety scores in patients participating in a symptom-driven remote arrhythmia monitoring program. Besides these strengths, there are limitations to acknowledge in this study. First, missing values are a common in questionnaire-based studies and could have led to selection bias. Second, the validity and reliability of the CaReQoL CHF questionnaire and PAM-13-NL questionnaire have not been identified for patients with cardiac arrhythmias. The evaluation of remote monitoring platforms requires validated questionnaires designed for remote monitoring platforms specifically. Overall, the data presented could be used to inform the design of a future randomized controlled trial comparing the effect of symptom-driven telemonitoring for cardiac arrhythmias on patient-reported outcomes. Remote monitoring programs for patients with cardiac arrhythmias could potentially mitigate a decline in self-management by intensifying contact with participants by using consistent feedback after self-measurements to avoid concerns and unanswered questions and improve patient education.

Conclusions

Symptom-driven remote arrhythmia monitoring does not seem to affect the HRQoL and sense of safety, whereas the perceived physical limitations tend to improve. This equivalence in patient-reported outcomes to usual care advocates for a broader implementation of such eHealth programs since this may improve accessibility and cost-effectiveness of healthcare. Patient-reported self-management declined during the first six months of participation showing the relevance of incorporating patient feedback and patient education.

Acknowledgements

We are grateful for all the participants in this study.

Conflicts of interest

No conflicts of interest.

REFERENCES

1. Leening MJG, Siregar S, Vaartjes I, et al. Heart disease in the Netherlands: a quantitative update. *Netherlands Hear J* 2014; 22: 3–10.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation. *Circulation* 2014; 129: 837–847.
3. Heeringa J, van der Kuip DAM, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; 27: 949–953.
4. Stewart S, Murphy N, Walker A, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004; 90: 286–292.
5. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013; 34: 2746–2751.
6. Thrall G, Lane D, Carroll D, et al. Quality of Life in Patients with Atrial Fibrillation: A Systematic Review. *Am J Med* 2006; 119: 448.e1–448.e19.
7. Son Y-J, Baek K-H, Lee SJ, et al. Health-Related Quality of Life and Associated Factors in Patients with Atrial Fibrillation: An Integrative Literature Review. *Int J Environ Res Public Health* 2019; 16: 3042.
8. Bubien RS, Knotts-Dolson SM, Plumb VJ, et al. Effect of Radiofrequency Catheter Ablation on Health-Related Quality of Life and Activities of Daily Living in Patients With Recurrent Arrhythmias. *Circulation* 1996; 94: 1585–1591.
9. Magnani JW, Wang N, Benjamin EJ, et al. Atrial Fibrillation and Declining Physical Performance in Older Adults. *Circ Arrhythmia Electrophysiol*; 9. Epub ahead of print May 2016. DOI: 10.1161/CIRCEP.115.003525.
10. Frederix I, Caiani EG, Dendale P, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019; 26: 1166–1177.
11. World Health Organisation. *A health telematics policy in support of WHO's Health-for-all strategy for global health development : report of the WHO Group Consultation on Health Telematics, 11-16 December, Geneva, 1997*. 1997.
12. Koole MAC, Kauw D, Winter MM, et al. First real-world experience with mobile health telemonitoring in adult patients with congenital heart disease. *Netherlands Hear J* 2019; 27: 30–37.
13. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–2962.
14. Van Kessel P, De Boer D, Hendriks M, et al. Measuring patient outcomes in chronic heart failure: Psychometric properties of the Care-Related Quality of Life survey for Chronic Heart Failure (CaReQoL CHF). *BMC Health Serv Res*; 17. Epub ahead of print 2017. DOI: 10.1186/s12913-017-2452-4.
15. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; 20: 1727–1736.
16. Rademakers J, Nijman J, van der Hoek L, et al. Measuring patient activation in the Netherlands: translation and validation of the American short form Patient Activation Measure (PAM13). *BMC Public Health* 2012; 12: 577.
17. Cardiology Centers of the Netherlands, https://www.cardiologiecentra.nl/en/your-privacy-and-cookies/ (2020).

18. Caceres BA, Hickey KT, Bakken SB, et al. Mobile Electrocardiogram Monitoring and Health-Related Quality of Life in Patients With Atrial Fibrillation. *J Cardiovasc Nurs* 2020; 35: 327–336.
19. Fairbrother P, Ure J, Hanley J, et al. Telemonitoring for chronic heart failure: The views of patients and healthcare professionals - a qualitative study. *J Clin Nurs* 2014; 23: 132–144.
20. Lu J-F, Chi M-J, Chen C-M. Advocacy of home telehealth care among consumers with chronic conditions. *J Clin Nurs* 2014; 23: 811–819.
21. Selder JL, Breukel L, Blok S, et al. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.
22. Botsis T, Hartvigsen G. Current status and future perspectives in telecare for elderly people suffering from chronic diseases. *J Telemed Telecare* 2008; 14: 195–203.
23. Middlemass JB, Vos J, Siriwardena AN. Perceptions on use of home telemonitoring in patients with long term conditions – concordance with the Health Information Technology Acceptance Model: a qualitative collective case study. *BMC Med Inform Decis Mak* 2017; 17: 89.
24. Kaufman DR, Patel VL, Hilliman C, et al. Usability in the real world: assessing medical information technologies in patients' homes. *J Biomed Inform* 2003; 36: 45–60.
25. Sanders C, Rogers A, Bowen R, et al. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. *BMC Health Serv Res* 2012; 12: 220.
26. Blok S, van der Linden EL, Somsen GA, et al. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; 2047487320957170.
27. Barmano N, Charitakis E, Karlsson J, et al. Predictors of improvement in arrhythmia-specific symptoms and health-related quality of life after catheter ablation of atrial fibrillation. *Clin Cardiol* 2018; clc.23134.
28. Semaan S, Dewland TA, Tison GH, et al. Physical activity and atrial fibrillation: Data from wearable fitness trackers. *Hear Rhythm* 2020; 17: 842–846.
29. Kodama S. Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women. *JAMA* 2009; 301: 2024.
30. Donald M, Ware RS, Ozolins IZ, et al. The role of patient activation in frequent attendance at primary care: A population-based study of people with chronic disease. *Patient Educ Couns* 2011; 83: 217–221.
31. Hibbard JH, Greene J, Overton V. Patients with lower activation associated with higher costs; Delivery systems should know their Patients' 'Scores'. *Health Aff* 2013; 32: 216–222.
32. Greene J, Hibbard JH. Why Does Patient Activation Matter? An Examination of the Relationships Between Patient Activation and Health-Related Outcomes. *J Gen Intern Med* 2012; 27: 520–526.
33. Begum N, Donald M, Ozolins IZ, et al. Hospital admissions, emergency department utilisation and patient activation for self-management among people with diabetes. *Diabetes Res Clin Pract* 2011; 93: 260–267.
34. Williams V, Price J, Hardinge M, et al. Using a mobile health application to support self-management in COPD: a qualitative study. *Br J Gen Pract* 2014; 64: e392–e400.
35. Guo Y, Chen Y, Lane DA, et al. Mobile Health Technology for Atrial Fibrillation Management Integrating Decision Support, Education, and Patient Involvement: mAF App Trial. *Am J Med* 2017; 130: 1388–1396.e6.

SUPPLEMENTARY MATERIALS

Supplementary Table S7.1: Comparison non-responders (n = 147) and responders (n = 109)

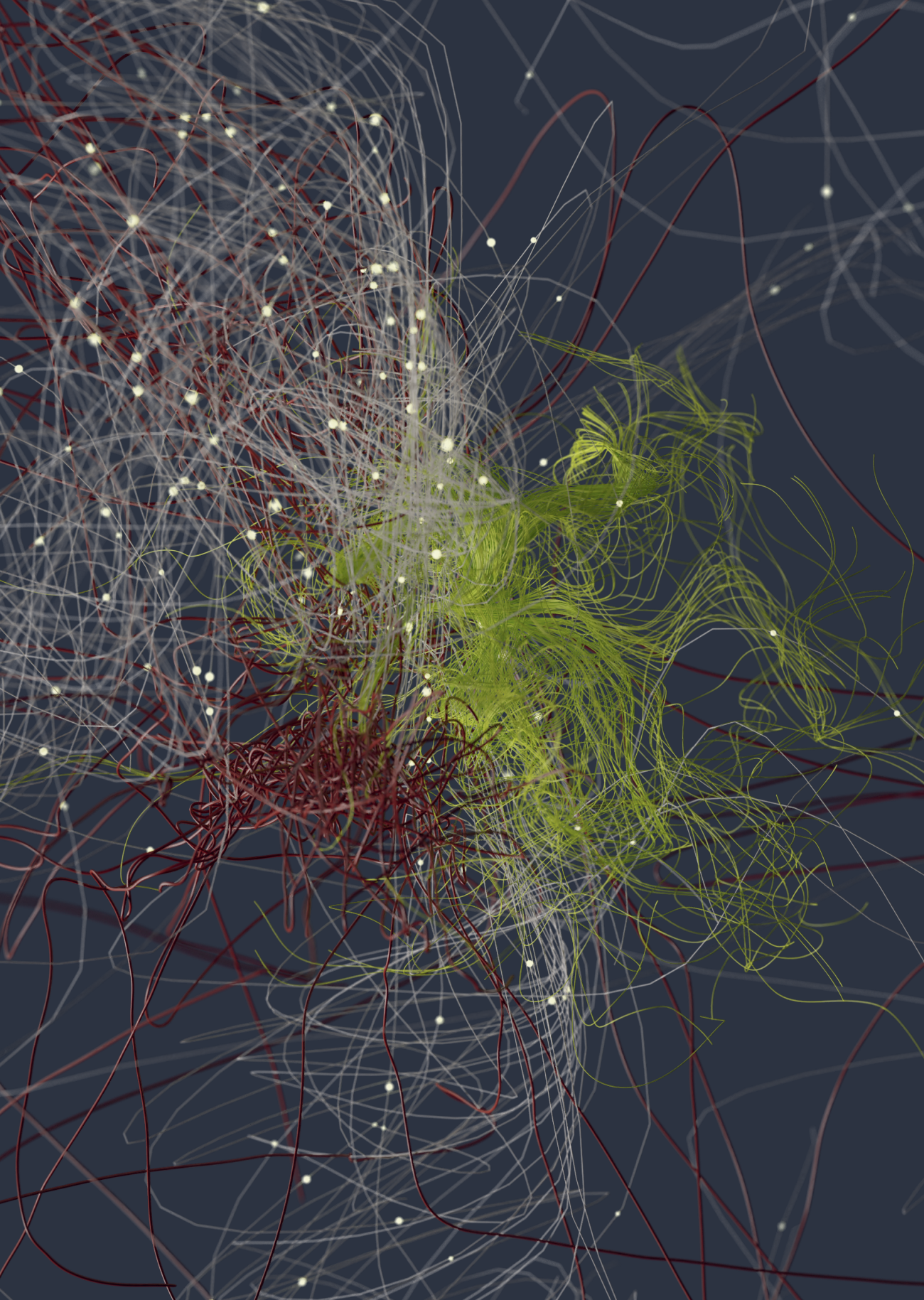
	Non-responders (n = 147)	Responders (n = 109)	p-value
Baseline characteristics			
Age	61.4 (13.2)	61.3 (10.9)	0.59
Gender, male	65 (46)	59 (41)	0.15
Number of medications	4.2 (3.0)	3.8 (3.0)	0.39
Body mass index	25.1 (3.9)	25.3 (4.0)	0.99
Psychiatric disorder	14 (10)	10 (9)	0.91
Cerebral vascular accident(s)	7 (5)	1 (1)	0.21
Chronic heart failure	7 (5)	3 (3)	0.41
Hypertension	57 (40)	45 (41)	0.61
Hypercholesterolemia	30 (21)	23 (21)	0.91
Diabetes mellitus	14 (10)	8 (7)	0.53
Diagnosis at start of HartWacht-program			0.008
First detected AF or unknown duration	21 (14)	24 (22)	
Paroxysmal AF	51 (35)	48 (44)	
Persistent AF	2 (1)	5 (4)	
Permanent AF	1 (1)	2 (2)	
Other[b]	72 (49)	30 (28)	
ECG recordings per months			
Total	1.80 [0.40-4.90]	2.40 [0.85-5.94]	0.153
Atrial fibrillation	0.00 [0.00-0.15]	0.04 [0.00-0.69]	< 0.001
Sinus rhythm	0.94 [0.20-3.06]	1.29 [0.30-3.37]	0.388
Other[c]	0.25 [0.00-1.10]	0.31 [0.09-1.04]	0.388
Baseline primary outcomes			
EQ5D Utility index	0.854 (0.14)	0.852 (0.13)	0.51
PAM-13-NL, level	3.06 (0.84)	3.45 (0.69)	< 0.001
CaReQoL HRQoL	3.92 (0.77)	4.04 (0.63)	0.29
Social emotional	4.07 (0.74)	4.06 (0.72)	0.84
Sense of safety	4.04 (0.78)	4.25 (0.71)	0.04
Physical limitations	3.96 (0.90)	3.92 (0.81)	0.51

[a] Independent-Samples Mann-Whitney U-test.
[b] This includes patients with palpitations of unknown origin, frequent premature atrial contractions and premature ventricular contractions.
[c] Premature atrial contractions, premature ventricular contractions, non-interpretable etc.

Supplementary Table S7.2: Comparison of the diagnosis in HartWacht-telemonitoring (n = 109) and standard care (n = 83)

	HartWacht-telemonitoring (n = 109)	Standard care (n = 83)	p-value
Diagnosis at start HartWacht-program			< 0.001
First detected or unknown duration AF	24 (22)	29 (35)	
Paroxysmal AF	48 (44)	35 (42)	
Persistent AF	5 (4)	8 (10)	
Permanent AF	2 (2)	11 (13)	
Other[a]	30 (28)	0 (0)	

AF = atrial fibrillation.
[a] This includes patients with palpitations of unknown origin, frequent premature atrial contractions and premature ventricular contractions.



Chapter 8

Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (EMPATHY); rationale and design

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Submitted – BMJ Open

ABSTRACT

Objective: Remote monitoring programs are effective in reducing blood pressure (BP) of hypertensive patients. However, examples that have been integrated in clinical practice and scaled up successfully are scarce. The Dutch HartWacht program is fully reimbursed and integrated. We aim to evaluate its feasibility, effectiveness, and potential to be scaled up successfully.

Design: Within the framework of the HartWacht program and as preparation for the EMPATHY trial we first assessed feasibility and identified predictors of treatment response. We then defined 24-hour BP and kidney function at six months follow-up as outcomes for the trial.

Participants: For the pilot analysis, data of 299 HartWacht participants (mean age 62 ± 10 years; 45% female) were analyzed. Within the EMPATHY trial, between January 2020 and April 2022, baseline data were collected from 130 patients (mean age 65 ± 10.3, 46% female).

Outcome measures: At baseline, office BP was 159 ± 22 (systolic) and 92 ± 12 (diastolic) mmHg and at six months follow-up home measured BP was 135 ± 13 and 135 ± 13 mmHg respectively. During the program, 196 (66%) participants achieved BP control for at least four consecutive measurements. We found no predictors for treatment response and observed that of patients not achieving BP control at three months, 21% did so at six months follow-up, while for 20% this was the other way around.

Conclusions: The HartWacht remote monitoring program is feasible for reducing BP in patients with hypertension. The lack of predictors for treatment response advocates for broad inclusion criteria for remote monitoring programs. Likewise, the considerable amount of patients changing between controlled and uncontrolled BP demonstrates the need for long term monitoring. To evaluate the effectiveness of HartWacht compared to usual care, and to explore the mechanisms that contribute to enhanced BP control in remote monitoring programs, we set up the EMPATHY trial.

Trial registration: https://www.trialregister.nl/trial/8353

INTRODUCTION

Hypertension is the most important modifiable risk factor for cardiovascular disease worldwide. However, despite the availability of adequate anti-hypertensive drugs, its cardiovascular complications have not been reduced, partly due to inadequacies in prevention, diagnosis and control [1]. Merely half of the adults with hypertension is aware of their condition, little over one in three were treated and as little as 14% had their blood pressure (BP) under control [2]. The emergence of new technologies can play an important role in improving these numbers [1,3]. Digital health and eHealth, and more specifically remote- or telemonitoring, are among the most promising emerging strategies to improve BP control and provide participants with the opportunity to remotely transfer personal data and BP readings [4].

Despite its promise, only few examples exist of large-scale remote monitoring programs for hypertension, integrated into daily practice with adequate reimbursement schemes, and questions remain about their effectiveness and associated costs [5,6]. Even in successful studies like the HYPERLINK trial, a little more than half of included participants achieved structural BP control during follow up [7]. Success factors for effective remote monitoring programs have been identified and include, among others, a large volume of connected patients and an intensive remote intervention with personalized feedback [8]. However, it remains unclear what type of individual predictors determine successful BP control.

The Dutch HartWacht program is a remote monitoring infrastructure and facilitates patients with, or at high risk of, cardiovascular disease [9–11]. Introduced in 2016, it is currently standard care in several outpatient cardiology clinics in the Netherlands.

To investigate the effectiveness of the HartWacht program in patients with uncontrolled hypertension we set up the *Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (EMPATHY)* study. EMPATHY is designed as an investigator initiated prospective, clinical trial that includes patients from the outpatient clinics of Cardiology Centers of the Netherlands, participating in the HartWacht hypertension program. In the present analysis we set out to assess determinants of treatment response in the HartWacht program and describe the rationale, design and baseline characteristics of the EMPATHY study.

METHODS

In preparation for the EMPATHY trial, we first assessed feasibility and identified predictors of treatment response in patients participating in the HartWacht remote monitoring program.

In the HartWacht program, patients with uncontrolled hypertension (office BP >140/90 mmHg and using anti-hypertensive medication) receive a iHealth Track™ BP monitor, validated for self-measurement [12]. The monitor is connected to the Heart for Health™ application on their own smart device (smartphone, tablet, or desktop). Through the application, remote measurements are integrated in the CardioPortal™ personal electronic patient file, which also contains medical history, medication use, allergies, and the details of physical examination and laboratory results. Patients start with a measurement week in which they measure twice in the morning and twice in the evening for seven days consecutively. After this week they continue to measure once a week. Measurements are checked by a dedicated health care team with access to the complete patient file. If values exceed pre-defined thresholds, patients are contacted by the team for swift therapeutic action, including medication titration or lifestyle advice. BP thresholds were defined as 140/90 mmHg. At the start of HartWacht, participants are scheduled for an intake consultation and after 4 months for an evaluation. In between, consultations take place whenever measurements structurally exceed the predefined thresholds. The HartWacht team undertakes action if two (lifestyle advice) or three (medication change) consecutive home measurements exceed the thresholds. HartWacht is set up as a monitoring program and continues until patients achieve structural BP control.

Study design and participants

All participants were referred by their general practitioner to one of the Cardiology Centers of the Netherlands (CCN) health centers, an organization of outpatient cardiology clinics in the Netherlands, were diagnosed with hypertension and used anti-hypertensive medication. The intervention group participated in the Dutch HartWacht home monitoring program for hypertension, which we compared with patients receiving usual care consisting of regular visits to their cardiologist. Patients were eligible for participation in the EMPATHY study if suffering from hypertension, despite the use of antihypertensive drugs. Patient were excluded if below 18 years of age, suffering from symptomatic heart failure or kidney failure or having had a recent (< 14 days) stroke or transient ischemic attack.

We first conducted a pilot to investigate how BP values in patients participating in the HartWacht program developed during six months after starting with home monitoring. We additionally studied all contact moments between patients and the HartWacht remote monitoring team and between patients and the treating cardiologist and the amount of BP measurements and of alarms generated by the measurements and scored the number of medication changes during follow-up by counting the times new drugs (dosages) were started and were ended. To assess predictors of successful BP control, we explored predictors of treatment success in the first 299 participants. We defined treatment success as achieving an average BP below 140/90 mmHg in four consecutive home measurements during follow-up (three and six months). Patients that failed to achieve BP control were labeled as non-responders. Parameters for comparison were based on previous research [13]. Binary variables included sex, diabetes, hyperlipidemia, hypertension medication use (0-2 vs. 3-6), and alcohol consumption (yes vs. no). Smoking was categorized as yes, no or ex-smoke. Age, body mass index (BMI), SBP and DBP at baseline and blood values creatinine, LDL and cholesterol were coded as continuous variables.

Based on the results of the pilot, we set up the Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (EMPATHY) study with the aim to assess whether, in comparison with usual care, the HartWacht home-monitoring program is effective. EMPATHY uses a pragmatic trial design to compare the effectiveness of home-monitoring on BP control in patients with difficualt to treat hypertension. We compare a cluster of patients that have insurance policies in which HartWacht participation is reimbursed to a cluster without this reimbursement. In the Netherlands, consumers have the right to switch between insurance companies and policies at the end of each calendar year [14]. At the start of the EMPATHY trial, around half of the big insurance companies decided to include HartWacht participation in their policies. Because it is part of the basic insurance package, the inclusion of HartWacht in the policy does not make the costs higher for the insured.

The primary outcome for the EMPATHY trial was defined as the reduction of systolic and diastolic BP (mmHg), measured with a 24-hour ambulatory BP monitor, between baseline and follow-up (6 months) compared to usual care. Secondary outcomes were the percentage of patients achieving BP control after 6 months, compared to usual care; the number of contact moments with the outpatient clinic (visits and telephone consults) and organ damage (microalbuminuria). The EMPATHY trial is registered at www.trialregister.nl under reference number NL8353.

Sample size calculation

With 80% power, assuming a standard deviation of 17 mm Hg and a difference of at least 7 mm Hg in systolic BP between HartWacht and usual care, based on earlier evaluation of the HartWacht program, an enrollment ratio of 2:1 and an attrition rate of 10-20% we estimated a sample size of 160 patients in the intervention group and 80 in the usual care group.

Data analysis and statistical methods

Continuous variables are presented as mean ± SD. Categorical variables are presented as frequencies and percentages. Continuous variables were tested for normality by visual analysis of histograms and Q-Q plots. Categorical variables were compared using the chi-square test or Fishers exact test and continuous variables using the t-test. A p-value of < 0.05 was considered statistically significant.

To evaluate characteristics that could differentiate between responders and non-responders, Kruskal-Wallis analysis was used. Missing values were imputed by mean imputation.

For these analyses R studio version 1.2.5019 with its inbuild statistic package as well as the "psych", "ggpubr", "ggfortify", and "ggplot2" packages, and SPSS software version 27.0 (IBM Corporation, Armonk, NY, USA) was used.

RESULTS

HartWacht database analysis

For the database analysis, data of 299 HartWacht participants (mean age 62±10 years; 45% female) were analyzed. At three months follow-up, 176 (59%) of all participants had their BP controlled and were labeled as responder. In between three- and six-months follow-up, 55 patients ended participation in HartWacht, in most cases either because BP control was achieved (n = 15) or because of lack of motivation (n = 26) (see Figure 8.1). At the time of data-extraction, 29 patients were still active but started less than six months, so they were excluded from analysis for six-months follow-up. Of the 215 patients still in the program at six month follow up, 128 (59%) were labeled as responder. Of the responders 45 (21%) were responder despite being non-responder at three-months follow-up. Likewise, 42 (20%) turned from responder to non-responder between three- and six-months follow-up.

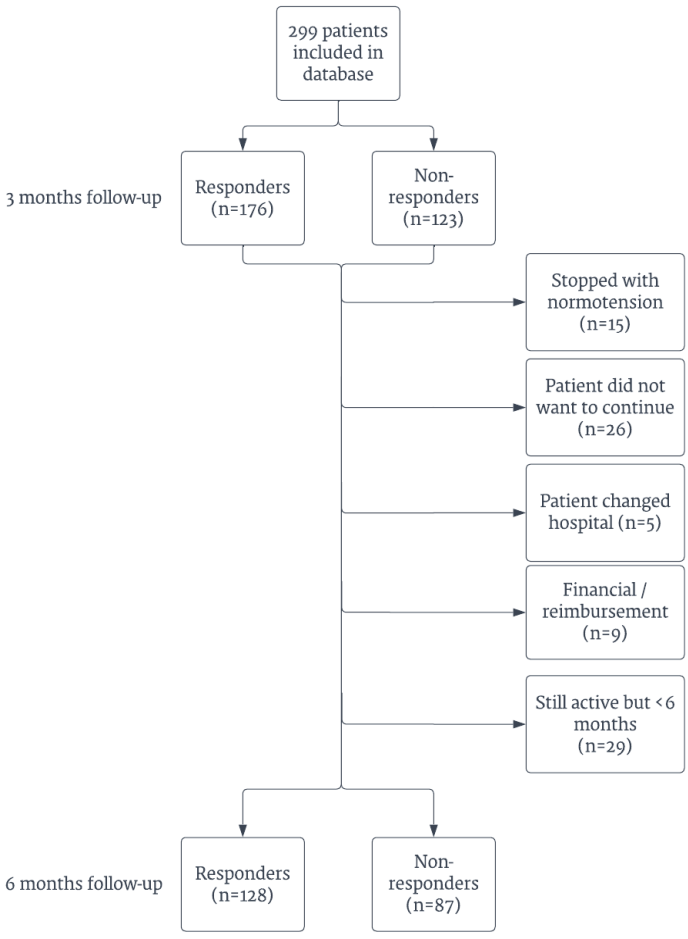


Figure 8.1: Inclusion and exclusion at three- and six-months follow-up for the retrospective database analysis.

Mean follow-up period was 26 ± 3 weeks. At baseline, office systolic BP was 159 ± 22 mmHg, while diastolic BP was 92 ± 12 mmHg with patients using an average of 2.1 ± 1.2 anti-hypertensive drugs. Systolic BP during the first month of home monitoring was 140 ± 15 mmHg and decreased to 135 ± 13 mmHg at 6 months follow-up. Average diastolic BP decreased from 86 ± 8 mmHg after one month to 83 ± 8 after 6 months (see Figure 8.2). During the program, 196 (66%) participants achieved a period of four consecutive BP measurements below 140/90 mmHg (see Figure 8.3) and 279 (93%) patients achieved at least one week of BP control.

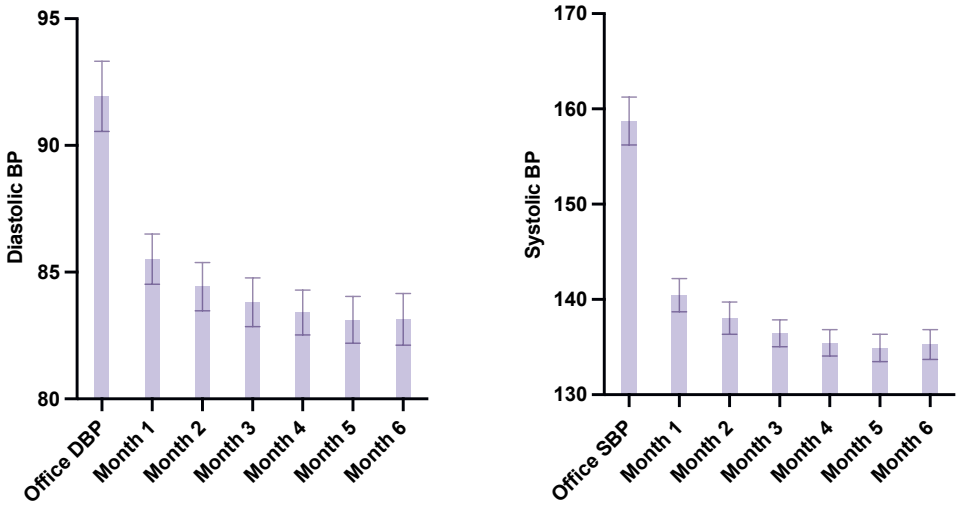


Figure 8.2: Mean systolic and diastolic blood pressure of patients at the last office measurement and the first six months of participating in the HartWacht program.

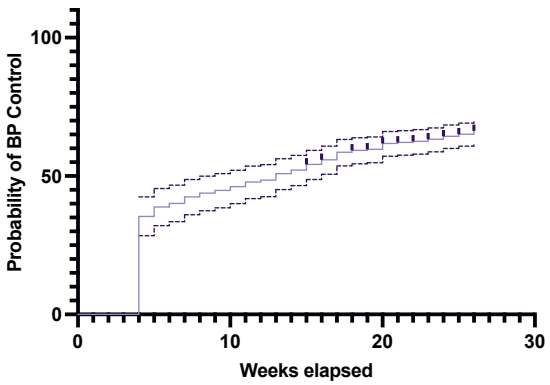


Figure 8.3: Patients participating in the HartWacht program blood pressure control or being excluded from the HartWacht program.

In the first month, HartWacht participants on average performed 17 ± 10 BP measurements, which decreased over time to 4 ± 4 monthly measurements in the sixth month (see Figure 8.4). This led to an average of 1.2 ± 0.8 consultations per patient in month 1, and 0.5 ± 1.5 consultations per patient in month 6. In month 5 the number of consultations peaked at 0.8 ± 1.4, caused by evaluation consultations planned after four months according to protocol. In other months the team offered an average of 0.5 consultations per patient (see Figure 8.4). During follow-up, patients underwent a total of 1.0 ± 1.7 medication changes.

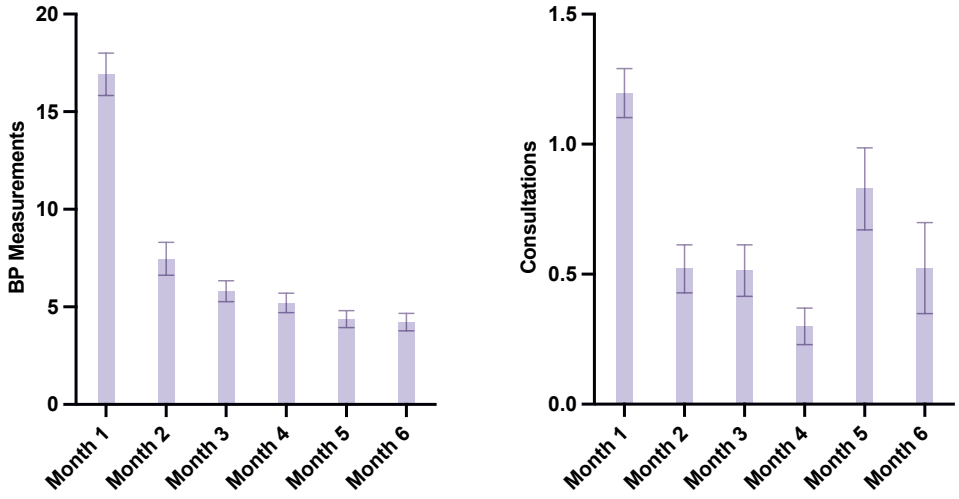


Figure 8.4: Mean number of home measurements and remote consultations of patients during the first six months of participating in the HartWacht program.

Patients that were defined as non-responders at three months follow-up had a higher office systolic BP at baseline than responders. No other significant differences were observed in patient characteristics between the responders and non-responders (see Table 8.1). During follow-up however, responders underwent less medication changes than non-responders. This difference was present both in the groups that were labeled responder and non-responder at three months (responders: 0.9 ± 1.5 and non-responders 1.3 ± 1.8 medication changes) and at six months (responders 0.8 ± 1.3 and non-responders 1.3 ± 1.7) follow-up (see Figure 8.5). Non-responders also started and ended their HartWacht participation with more anti-hypertensive medication than responders, although this difference was not significant (see Figure 8.5).

EMPATHY cohort profile

Between January 2020 and April 2022, baseline EMPATHY data were collected among patients participating in the HartWacht hypertension program and patients in usual care. Data were collected on one of the outpatient clinics of Cardiology Centers of the Netherlands. All participants provided written informed consent. For baseline characteristics, see Table 8.2. No significant differences were observed between the HartWacht and usual care. Most patients used three different classes of medication at baseline, as presented in Table 8.3. The 24-hour BP measurement at baseline showed elevate values for both groups (see Table 8.4).

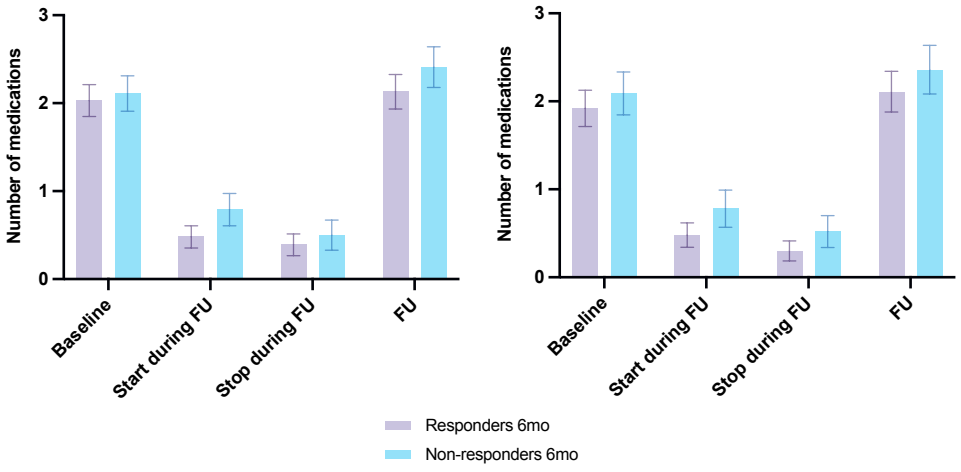


Figure 8.5: Anti-hypertensive medication at baseline per patient, changes during follow-up and medication at follow-up.

Table 8.1: HartWacht non-responders and responders after three and six months follow up

	3 months FU			6 months FU		
Variable	Non-responder (n = 123)	Responder (n = 176)	p-value	Non-responder (n = 87)	Responder (n = 128)	p-value
Female, n (%)	60 (49)	75 (43)	0.349	35 (40)	61 (48)	0.350
Age [years] (mean ± SD)	63 ± 10	62 ± 11	0.193	62 ± 11	63 ± 10	0.357
BMI (mean±SD)	29.4 ± 4.9	28.1 ± 4.6	0.026	29.1 ± 5.2	28.3 ± 4.4	0.204
Office SBP [mmHg] (mean ± SD)	162 ± 23	157 ± 21	0.044	159 ± 22	160 ± 22	0.873
Office DBP [mmHg] (mean ± SD)	92 ± 13	92 ± 12	0.819	91 ± 14	93 ± 11	0.250
DM, n (%)	18 (15)	24 (14)	0.940	20 (23)	13 (10)	0.018
Dyslipidaemia, n (%)	30 (24)	60 (34)	0.095	25 (29)	32 (25)	0.651
Smoking, n (%)	69 (56)	95 (54)	0.807	47 (54)	71 (56)	0.945
Alcohol [units/day] (mean ± SD)	0.69 ± 1.22	0.77 ± 1.29	0.595	0.62 ± 1.02	0.87 ± 1.40	0.154
Creatinine (mean ± SD)	80 ± 22	78 ± 18	0.356	79 ± 21	79 ± 20	0.865
HT Medication (mean ± SD)	2.11 ± 1.13	2.03 ± 1.21	0.538	2.09 ± 1.15	1.92 ± 1.18	0.296
HT Medication > 2, n (%)	47 (38)	71 (40)	0.802	34 (39)	46 (35)	0.746

Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute numbers and percentages.
FU, follow-up; BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HT, hypertension.

Table 8.2: Baseline characteristics and medical history EMPATHY participants

Variable	All (n = 130)	HartWacht (n = 91)	UC (n = 39)	p-value
Female, n (%)	63 (48.5)	42 (46.2)	21 (53.8)	0.421
Age [years] (mean ± SD)	65.2 ± 10.3	64.1 ± 10.0	66.9 ± 11.1	0.237
BMI (mean ± SD)	30.0 ± 5.1	29.5 ± 4.7	30.6 ± 5.8	0.324
Office SBP [mmHg] (mean ± SD)	163.0 ± 20.5	162.6 ± 19.7	165.3 ± 22.6	0.391
Office DBP [mmHg] (mean ± SD)	92.5 ± 11.7	93.2 ± 10.2	92.3 ± 14.6	0.921
uACR (mg/mmol)	1.2 [2.2]	1.2 [2.2]	1.5 [3.1]	0.206
DM, n (%)	40 (30.8)	28 (30.8)	12 (30.8)	1.000
Dyslipidemia, n (%)	60 (46.2)	41 (45.1)	19 (48.7)	0.701
Myocardial infarction, n (%)	8 (6.2)	7 (7.7)	1 (2.6)	0.434
Transient ischemic attack, n (%)	7 (5.4)	2 (2.2)	5 (12.8)	0.025
CABG, n (%)	9 (6.9)	5 (5.5)	4 (10.3)	0.451
PCI, n (%)	14 (10.8)	10 (11.0)	4 (10.3)	1.000
CAG, n (%)	25 (19.2)	19 (20.9)	6 (15.4)	0.466
Family history of CVD, n (%)	77(59.7)	55(60.4)	22 (57.9)	0.954
Smoking, n (%)				0.206
No	73 (56.6)	47 (51.6)	26 (68.4)	
Yes	12 (9.3)	9 (9.9)	3 (7.9)	
Former smoker	44 (34.1)	35 (38.5)	9 (23.7)	
Alcohol consumption, n (%)				0.810
No	63 (48.8)	44 (48.4)	19 (50.0)	
Yes	65 (50.4)	46 (50.5)	19 (50.0)	
Former alcohol consumer	1 (0.8)	1 (1.1)	0	
Frequency alcohol consumption, n (%)				0.510
Moderate drinker	63 (48.8)	44 (34.1)	19 (50.0)	
Occasional excessive drinker	2 (1.55)	2 (2.20)	0	
Frequent excessive drinker	0	0	0	

Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute numbers and percentages.
The p-values reflect the comparison of HartWacht patients vs. usual care patients.
UC, usual care; SBP, systolic blood pressure; DBP, diastolic blood pressure; CABG, Coronary Artery Bypass Graftin; PCI, Percutaneous coronary intervention; CAG, coronary angiography; CVD, cardiovascular disease.

DISCUSSION

We evaluated the effectiveness a reimbursed program for remote monitoring of BP and tried to identify predictors of success. We show that at six-months follow-up, participants of the HartWacht program had a significant decrease in BP compared to baseline. Overall, 66% demonstrated a period of four consecutive BP measurements below 140/90 mmHg during participation. The rate of patients achieving normotension was the highest in the first weeks after starting the program, likely caused by adaptation of drug therapy at the last office visit, just before starting the HartWacht program. At

three- and six-months follow-up 59% of participants achieved BP control. Around 20% of participants changed from responder to non-responder, or vice versa, between the two follow-up moments. This demonstrates that BP control varies in time. Participants that achieved BP control were still likely to have one or more weeks with elevated values during participation. Other factors can impact BP over time, we know that next

Table 8.3: Antihypertensive drugs at baseline

Variable	All (n = 130)	HartWacht (n = 91)	UC (n = 39)	p-value
Classes of antihypertensive drugs, n (%)				0.230
1	7 (5.4)	7 (7.7)	0	
2	13 (10.0)	11 (12.1)	2 (5.1)	
3	81 (62.3)	53 (58.2)	28 (71.8)	
4	28 (21.5)	19 (20.9)	9 (23.1)	
5	1 (0.8)	1 (1.1)	0	
ACE inhibitor, n (%)	50 (38.4)	37 (38.0)	13 (33.4)	0.551
Beta-blocker, n (%)	78 (60.0)	51 (56.0)	27 (69.2)	0.160
ARB, n (%)	66 (50.8)	43 (47.3)	23 (59.0)	0.352
Alpha-blocker, n (%)	11 (8.5)	8 (8.8)	3 (7.7)	0.570
Calcium channel blocker, n (%)	93 (71.6)	65 (71.4)	28 (71.8)	0.803
Diuretic, n (%)	94 (72.3)	65 (71.4)	29 (74.4)	0.939
Other antihypertensive drugs, n (%)	0	0	1 (2.6)	0.300

Categorical variables are presented as absolute numbers and percentages.
The p-values reflect the comparison of HartWacht patients vs. usual care patients.
UC, usual care; ARB, angiotensin II receptor blocker.

Tabel 8.4: Average ambulatory blood pressure values at baseline

Variable	All (n = 125)	HartWacht (n = 86)	UC (n = 39)	p-value
24 hours systolic BP	144.2 ± 21.5	143.4 ± 20.8	145.0 ± 22.3	0.792
24 hours diastolic BP	79.2 ± 13.1	79.7 ± 11.8	77.7 ± 15.4	0.375
Daytime Systolic BP	147.4 ± 22.0	146.3 ± 21.6	148.9 ± 22.3	0.632
Daytime diastolic BP	81.4 ± 13.4	81.8 ± 12.4	80.0 ± 15.2	0.435
Nighttime Systolic BP	136.3 ± 24.0	135.7 ± 21.9	137.6 ± 28.3	0.681
Nighttime diastolic BP	71.8 ± 14.7	72.6 ± 13.2	70.0 ± 17.6	0.363
Quality 24h BP monitoring, n (%)				0.457
Good	89 (71.2)	64 (74.4)	25 (64.1)	
Average	27 (21.6)	16 (18.6)	11 (28.2)	
Bad	9 (7.2)	6 (7.0)	3 (7.7)	

Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute numbers and percentages.
The p-values reflect the comparison of HartWacht patients vs. usual care patients.
UC, usual care; BP, blood pressure.

to patient related factors seasonal variations may influence BP control over time, as evidenced by studies that show that BP tends to be lower in summer compared to winter [15]. To manage this variety and keep BP within thresholds structurally, remote BP monitoring programs are eminently suited.

For non-responders, the number of anti-hypertensive drug changes was higher than for responders, which is expected because when BP is under control no adaptation of therapy is needed. Despite multiple changes in drug therapy, BP lowered insufficiently. For these participants, the lack of BP control is likely to have other causes than physician inertia including an inability to comply with the medication scheme.

To further improve effectiveness of the HartWacht program we aimed to identify success factors associated with BP control in patients referred to outpatient cardiology clinics. We found no differences between patients that had their BP controlled during follow-up and patients that were unsuccessful in doing so. To further investigate the specific effect of HartWacht participation compared to usual care, we designed the EMPATHY trial. Because we did not identify patient characteristics that contribute to successful response to the program, we applied broad inclusion criteria for the trial.

In earlier research, like the TASMINH, HYPERLINK and HOME BP studies, remote BP monitoring was compared with usual care, consisting of routine visits to their clinic or GP, at the discretion of the physician and according to guidelines, which in general suggest annual consultations to check BP and discuss lifestyle and drug therapy [7,16–18]. They demonstrated effectiveness of such programs in reducing BP of hypertensive patients and increasing the number of patients achieving BP control. Additionally, as described earlier, when success factors are taken into account in their design and implementation they can also be cost-effective [8,19]. However, large scale implementation in daily practice with structural reimbursement is scarce. In the present study, we describe results from an integrated remote monitoring program that is part of clinical routine, which is covered by the national basic insurance package. It therefore demonstrates the potential of such a remote monitoring program to be scaled up successfully.

To further evaluate the effectiveness of the HartWacht hypertension program, a comparison with usual care is mandatory, in order to investigate to what extend the effect can be attributed to remote monitoring. Various factors can contribute to this BP reduction in time: earlier research, like the studies mentioned above, demonstrated improved adherence to BP-medication and decreased clinician inertia in a remote monitoring group compared to usual care [20–22]. Besides those factors, both the white coat effects and regression to the mean may result in a spontaneous BP reduction.

The white coat effect, broadly defined as an anxiety response associated with the measurement of BP, is generally less pronounced in patients measuring their BP at home. However, anticipatory reactions to the self-measurement of BP still result in higher BP values as demonstrated by the higher average BP values during home BP measurement as compared to ambulatory BP measurements [23]. In addition, regression to the mean effects in individuals with high BP values who are at the right side of the Gaussian distribution curve at the time of enrollment, usually have a tendency to shift to the mean during subsequent measurements based on chance alone. Recent research demonstrated that this regression to the mean effect can also be observed during home BP measurement, although the effect is less pronounced compared to office BP readings [24]. Overall, in research on effectiveness of remote monitoring, several factors impacting BP play a role in the intervention group or control group. In trials like TASMINH and HYPERLINK the usual care group is loosely instructed, telling participants to work with their physicians as they had before, or asking them to attend the family doctor once for medication review at baseline [7,25]. Comparing remote monitoring with usual care as it is, at the discretion of the physician and according to guidelines, will still give the best insight in its effectiveness.

EMPATHY uses a pragmatic trial design, in which we compare two clusters of patients, one with insurance coverage for HartWacht and one without. This type of cluster design may cause bias, although there is no known difference in patient preferences or costs between insurance. Additionally, the four largest insurance companies represent 85% of Dutch citizens and all have a varied clientele spread throughout the country, although some concerns have regional increased presence. In our study, we see no differences in baseline characteristics, so risk of bias is limited.

EMPATHY participants do not receive compensation for participation. We therefore expect 10-20% loss to follow-up, which would be comparable with studies of similar design [7,16–18]. As patients showing normotension with home measurements are more likely to not undergo the 24h measurement, we expect the loss to follow up to have a diminishing impact on the size of the effect we will evaluate.

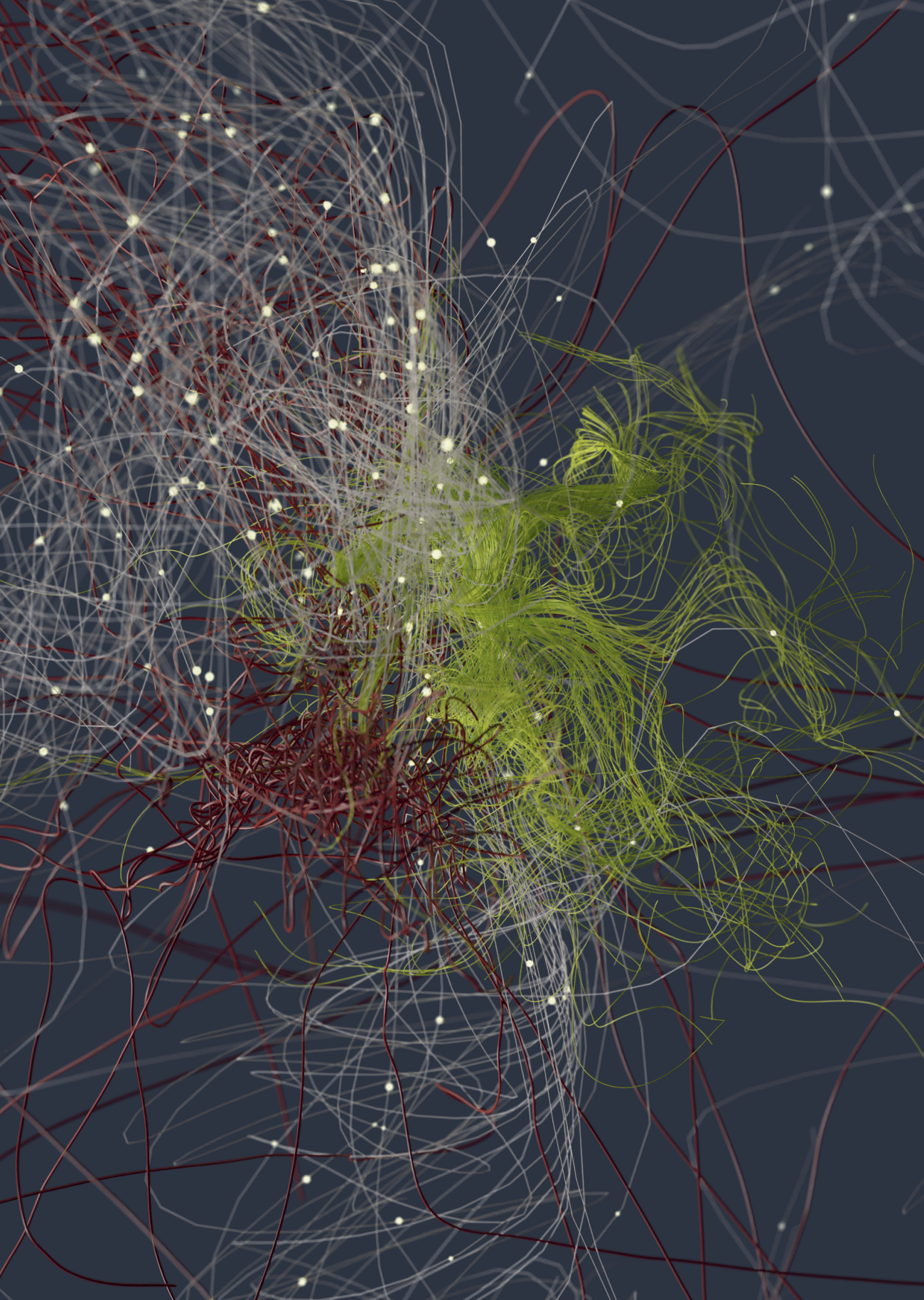
Conclusion

The HartWacht remote monitoring program is feasible for reducing BP in patients with hypertension despite the use of anti-hypertensive medication. To evaluate its effectiveness compared to usual care, and to explore the mechanisms that contribute to enhanced blood BP in remote monitoring programs, we set up the EMPATHY trial.

REFERENCES

1. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet* 2016; 388: 2665–2712.
2. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control. *Circulation* 2016; 134: 441–450.
3. Tucker KL, Earle K, Bray EP, et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. *PLOS Med* 2017; 14: e1002389.
4. Frederix I, Caiani EG, Dendale P, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019; 26: 1166–1177.
5. Omboni S, Gazzola T, Carabelli G, et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring. *J Hypertens* 2013; 31: 455–468.
6. Jacob V, Chattopadhyay SK, Proia KK, et al. Economics of Self-Measured Blood Pressure Monitoring: A Community Guide Systematic Review. *Am J Prev Med* 2017; 53: e105–e113.
7. Margolis KL, Asche SE, Bergdall AR, et al. Effect of Home Blood Pressure Telemonitoring and Pharmacist Management on Blood Pressure Control. *JAMA* 2013; 310: 46.
8. Blok S, van der Linden EL, Somsen GA, et al. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; 2047487320957170.
9. Selder JL, Breukel L, Blok S, et al. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.
10. Wierda E, Blok S, Somsen GA, et al. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of Hartwacht as a learning case. *BMJ Innov* 2020; 6: 170–176.
11. Kolk MZH, Blok S, De Wildt MCC, et al. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal*. Epub ahead of print 9 March 2021. DOI: 10.1093/ehjdh/ztab030.
12. The dabl® Educational Trust Limited. Blood pressure monitors - Validations, papers and reviews. http://www.dableducational.org/sphygmomanometers/recommended_brand.html (accessed 21 May 2022).
13. Asche SE, O'Connor PJ, Dehmer SP, et al. Patient characteristics associated with greater blood pressure control in a randomized trial of home blood pressure telemonitoring and pharmacist management. *J Am Soc Hypertens* 2016; 10: 873–880.
14. Maarse H, Ter Meulen R. Consumer Choice in Dutch Health Insurance after Reform. *Heal Care Anal* 2006; 14: 37–49.
15. Stergiou GS, Palatini P, Modesti PA, et al. Seasonal variation in blood pressure: Evidence, consensus and recommendations for clinical practice. Consensus statement by the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. *J Hypertens* 2020; 38: 1235–1243.
16. McManus RJ, Mant J, Roalfe A, et al. A randomised controlled trial of patient held targets and self monitoring in the control of hypertension. *Am J Hypertens* 2005; 18: A90, Abstract no: P233.

17. Franssen M, Farmer A, Grant S, et al. Telemonitoring and/or self-monitoring of blood pressure in hypertension (TASMINH4): protocol for a randomised controlled trial. *BMC Cardiovasc Disord* 2017; 17: 58.
18. McManus RJ, Mant J, Franssen M, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *Lancet* 2018; 391: 949–959.
19. McManus RJ, Little P, Stuart B, et al. Home and Online Management and Evaluation of Blood Pressure (HOME BP) using a digital intervention in poorly controlled hypertension: Randomised controlled trial. *BMJ* 2021; 372: 1–13.
20. Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control a cluster randomized clinical trial. *JAMA - J Am Med Assoc* 2013; 310: 46–56.
21. Bryant KB, Sheppard JP, Ruiz-Negrón N, et al. Impact of Self-Monitoring of Blood Pressure on Processes of Hypertension Care and Long-Term Blood Pressure Control. *J Am Heart Assoc*; 9. Epub ahead of print 4 August 2020. DOI: 10.1161/JAHA.120.016174.
22. Fletcher BR, Hartmann-Boyce J, Hinton L, et al. The Effect of Self-Monitoring of Blood Pressure on Medication Adherence and Lifestyle Factors: A Systematic Review and Meta-Analysis. *Am J Hypertens* 2015; 28: 1209–1221.
23. Berkhof RT, Gazzola K, van den Born B-JH. Effect of self-initiated and fully-automated self-measurement on blood pressure. *J Hum Hypertens* 2020; 34: 176–183.
24. Wang N, Atkins ER, Salam A, et al. Regression to the mean in home blood pressure: Analyses of the BP GUIDE study. *J Clin Hypertens* 2020; 22: 1184–1191.
25. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010; 376: 163–172.



Chapter 9

The Corona pandemic paves the way for eHealth innovations - Digitalization and self-management in cardiovascular care benefit from the pandemic

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ABSTRACT

The Covid pandemic paves the way for digital innovations in healthcare. Nevertheless, not all of them succeed. The implementation of a smartphone cardiology application demonstrates the opportunities and risks.

INTRODUCTION

During the start of the corona pandemic healthcare was under significant pressure, leading to an increase in the use of teleconsultation and videocalls [1]. We demonstrate how digitalization of first line cardiovascular care in Amsterdam accelerated, partly due to the Covid-19 pandemic. This could be a breakthrough for the organization of chronic first line care.

PATIENT APPLICATION

With almost 18 million people dying from cardiovascular disease annually, it is the leading cause of death globally. Elevated blood pressure (hypertension) is its most important risk factor [2]. In the Netherlands, yearly tens of thousands of people die from complications of cardiovascular disease and hypertension care is, despite all efforts on prevention, lifestyle and treatment, still suboptimal [3,4].

Preliminary results of our research show that general practitioners (GPs) don't always adhere to guidelines for hypertension management and treatment of cardiovascular disease. For instance, patients with different ethnical backgrounds frequently get the wrong medicine prescribed. Recent research shows however, that blood pressure control improved in patients that managed their own antihypertensive medication [5].

Partly based on this research, general practitioners (ROHA), cardiologists (Cardiology Centers of the Netherlands), software developers (Heart for Health) and health care innovators (AHTI) set up the DHoTS (Digital Health, from Technology to Services) project, aiming to improve cardiovascular care for patients and careproviders [6]. In this project a patient application was developed for self-monitoring of blood pressure by patients, together with an integrated digital healthcare service for the general practitioner. Based on remote measurements and patient characteristics (lifestyle factors such as smoking and clinical parameters such as blood and urine values) a risk classification is calculated, including treatment advice based on the latest cardiovascular risk management guidelines [7]. The general practitioner or assistant can then decide to take over the automatically generated advice or deviate from it. By registering this decision in the platform, including reason why, the system learns and improves its decision making.

Since one and a half year, general practices in Amsterdam in geographically and socioeconomically different neighborhoods join the project to cooperate in developing

this digital health service. Despite financial compensation and organizational support, it appeared to be challenging for the practices to embrace this innovation next to the daily practice. Besides the necessity of improving technical elements in the portal, we also observed a mental barrier in both patients and general practitioners and assistants to step away from regular care and let digital care take over.

eHEALTH ADOPTION

Since the beginning of the Covid-19 pandemic the number of patients using the digital health service increased (see Figure 9.1). Several elements seem to have contributed to the accelerated inclusion in the DHoTS program; and different factors have impacted the eHealth adoption among general practitioners [8]:

1. First, corona measures focused on minimizing physical contact heavily impacted the daily practice, including cardiovascular risk management. Healthcare was deemed to be organized differently to treat patients remotely. Additionally, because patients stayed away from the practice, time pressure on the healthcare providers decreased. Therefore, general practitioners and assistants could focus on adapting processes to the eHealth functionalities.
2. General practitioners and physician assistants had more time to provide instructions, increasing the willingness of patients to start using the eHealth initiative. Better education about the system and procedures is essential for effective use and acceptance of eHealth by patients.
3. Awareness was high among patients about the limited availability of regular healthcare. This increased motivation to integrate eHealth into daily life.
4. The increase of users of the application motivated the developers to accelerate technical improvements in the application, to support this unique growth. The contact between healthcare provider and software developer intensified to discuss in detail how to solve practical or technical bugs.
5. To be able to handle the increased demand for the eHealth service, the general practices that participated in the DHoTS project were supported in implementing the service and instructing and activating patients. This transformation, from product to service, during the pandemic, directly led to an increase in connected patients. Arguably, healthcare providers embraced the innovation more easily because administrative and technical tasks could be handed over to others.

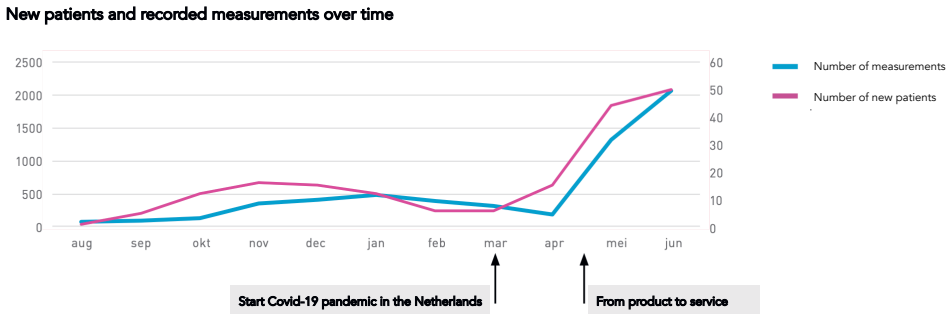


Figure 9.1: Patients and blood pressure measurements per month from August 2019 to June 2020.

SUCCESS FACTORS

Obviously, this new digital care delivery and accompanying changing organization lead to a different cost structure. Afterall, more blood pressure monitors are needed, as well as a new IT-infrastructure. Additionally, compared to traditional non-digital healthcare, much more datapoints are available that can impact medical policy and therefore need to be processed. On the other hand, increased blood pressure control will lead to a decrease in cardiovascular complications and less healthcare costs. For the general practice, the automatization causes a decrease in personnel costs.

Evidence on cost-effectiveness of remote monitoring programs for blood pressure management is heterogeneous [9,10]. However, scientific literature describes multiple examples of initiatives that demonstrate considerable effect on blood pressure against very limited costs. We identified three factors that successful programs have in common [11]:

1. Remote measurements are followed by an active intervention with personalized feedback
2. Regular care is at least partially replaced by remote measurements
3. Many patients participate

It appears from these three factors that in the starting phase, with high investment costs and a small but growing group of participating patients, it is too early to evaluate cost-effectiveness of the current activities. The partners invested in setting up the program, backed by a European subsidy. When more patients participate in a program (shared between multiple practices) and the care delivery organization is adapted to that, a financially sustainable situation arises in which revenues outweigh costs from the perspective of healthcare provider, insurer, and society.

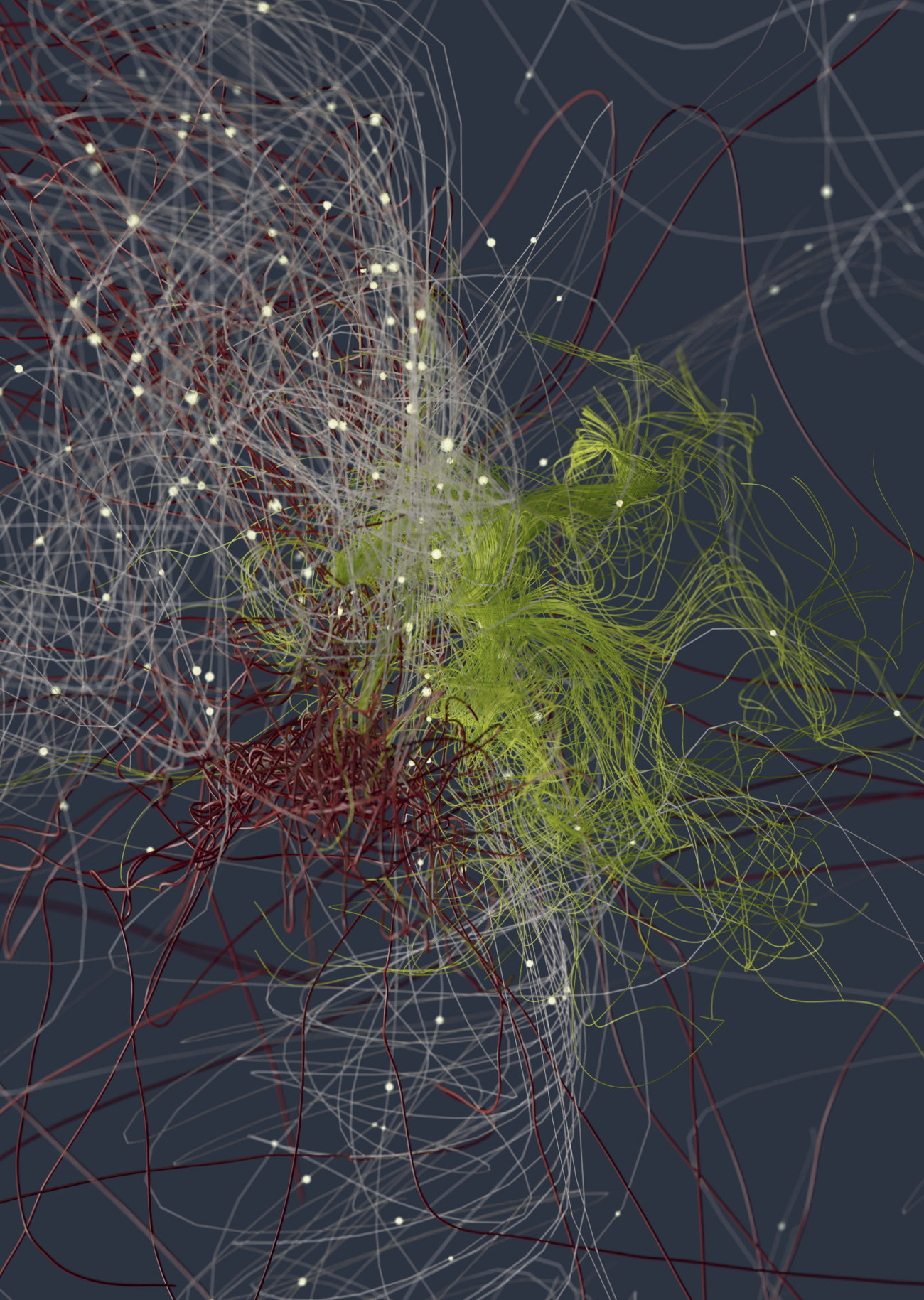
SENSE OF URGENCY

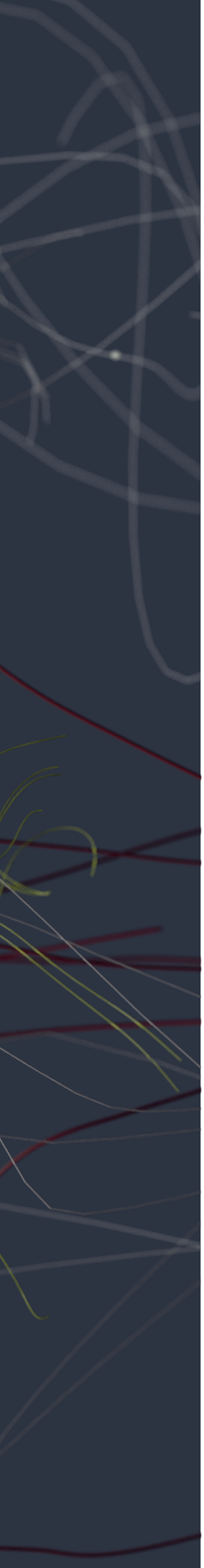
Because the use of eHealth increased during the Covid-19 pandemic, we were able to identify factors that are crucial for the acceptance of this form of healthcare by general practitioner and patient. Obviously, in a different situation it is challenging to create the same sense of urgency in healthcare providers and patients to exchange regular care for digital innovations. Habits and routines sometimes block improvements. Possibly, the ongoing threat of new outbreaks stimulates the urgency for other innovations in healthcare. Additionally, we observed that factors like availability of time of the healthcare provider and practical support for the implementation on the patient side are crucial for the uptake of a digital service. While implementing eHealth programs, these factors should be recognized and dealt with to achieve sustainable and scalable healthcare. Hopefully, we don't need new outbreaks to continue this acceleration of innovations.

REFERENCES

1. Wouters M, Huygens M, Voogdt H, Meurs M, Groot J De, Lamain A, Bruin K De, Brabers A, Hofstede C, Friele R, Gennip L Van. Samen aan zet! eHealth-monitor 2019. Den Haag en Utrecht; 2019.
2. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Abate KH, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P, Banerjee A, Bärnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, Catalá-López F, Feigin VL, Fernandes JC, Fischer F, Gebru AA, Gona P, Gupta R, Hankey GJ, Jonas JB, Judd SE, Khang YH, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115mmHg, 1990-2015. *JAMA - J Am Med Assoc* 2017; 317: 165–182.
3. Hartstiching De. Cijfers hart- en vaatziekten. 2020. https://www.hartstichting.nl/hart-en-vaatziekten/feiten-en-cijfers-hart-en-vaatziekten (24 July 2020)
4. Schelleman H, Klungel OH, Kromhout D, Boer A de, Stricker Bhc, Verschuren WMM. Prevalence and determinants of undertreatment of hypertension in the Netherlands. *J Hum Hypertens* 2004;18:317–324.
5. Verhage S, Blok S, Vijver S Van de, Winter MM, Born B-J van den. Evaluation of Cardiovascular Risk Management and Validation of a Decision Support System for the Management of Hypertension in Dutch General Practices. Amsterdam University Medical Centers, Location AMC; 2019.
6. Jowett S, Jones MI, Penaloza C, Bryan S, Schwartz C, Haque MS, Greenfield SM, Little P, Shackleford H, Mant J, Varghese J, Hobbs FDR, Williams B, Shovelton C, Bray EP, McManus RJ. Effect of Self-monitoring and Medication Self-titration on Systolic Blood Pressure in Hypertensive Patients at High Risk of Cardiovascular Disease. *Jama* 2014; 312: 799.
7. NHG. Cardiovasculair Risicomanagemt - NHG Richtlijnen. Utrecht; 2018.
8. European Commission. eHealth adoption in primary healthcare in the EU is on the rise. Brussels; 2019.

9. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring. *J Hypertens England* 2013; 31: 455–468.
10. Jacob V, Chattopadhyay SK, Proia KK, Hopkins DP, Reynolds J, Thota AB, Jones CD, Lackland DT, Rask KJ, Pronk NP, Clymer JM, Goetzel RZ. Economics of Self-Measured Blood Pressure Monitoring: A Community Guide Systematic Review. *Am J Prev Med Netherlands* 2017; 53: e105–e113.
11. Blok S, Linden EL van der, Somsen GA, Tulevski II, Winter MM, Born B-JH van den. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; 2047487320957170.





Chapter 10

Discussion

THE PROMISE OF eHEALTH

Disappointing long-term benefits of treatment of cardiovascular disease are not caused by a lack of therapeutical options, as effective and cheap treatment is widely available, but rather by low uptake in clinical practice, including physician inertia, and non-adherence of patients [1]. The main challenge for our aging society with increasing chronic diseases is to effectively deliver evidence-based therapy to the ones that need it. Over the past decades, eHealth has been suggested as the delivery strategy to overcome this shortcoming: patients would become well informed managers of their own health, while clinicians would turn into "telecarers" [2]. Moreover, initiatives such as telemedicine would improve access, enhance quality and contain costs of healthcare [3]. But even though evidence is growing on the effectiveness of remote monitoring for hypertension and the benefits of eHealth have been clearly demonstrated during the COVID pandemic, eHealth programs for cardiovascular disease have only partly lived up to its expectations, as uptake in clinical practice remains limited [4,5].

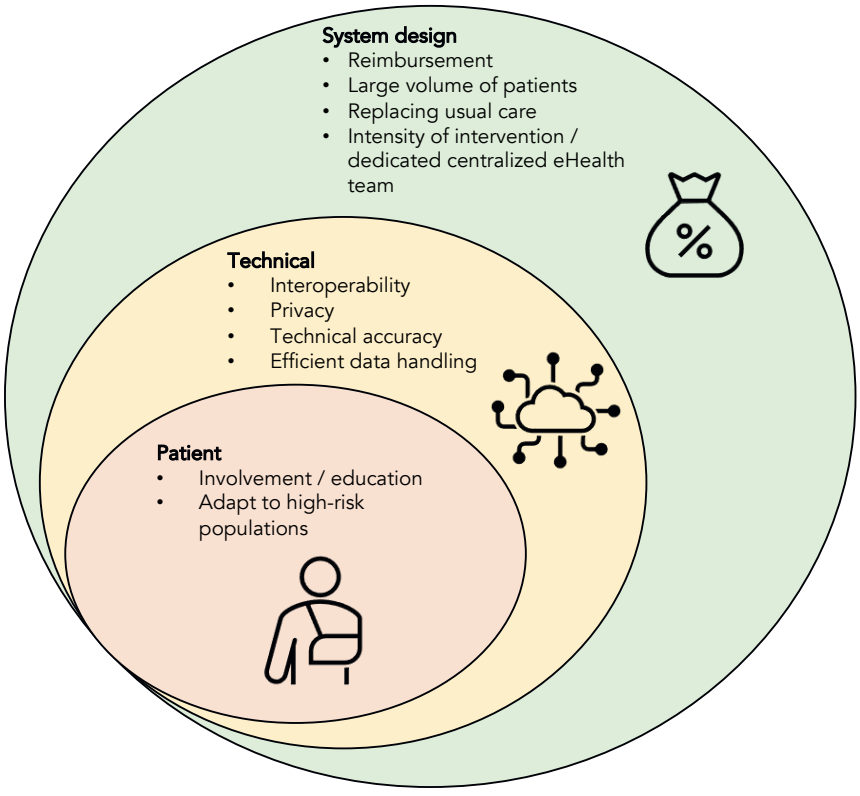


Figure 10.1: Success factors for scalable eHealth solutions.

CURRENT SUCCESS FACTORS

The Dutch HartWacht program, launched in 2016, is an example of a successfully integrated eHealth initiative that has been scaled up over the years [6–9]. Currently, around 7,000 patients from 13 clinics throughout the Netherlands have participated [10]. Generalizable success factors that characterize the HartWacht program, as described in this thesis, are divided in three categories: i) aspects of the health system in which eHealth operates, ii) technical requirements of the eHealth infrastructure and iii) patient related aspects (see Figure 10.1).

FUTURE PERSPECTIVE

The continuing development of more advanced, user-friendly digital health devices focused on the consumer market will increase uptake of health measurements by the public. However, up until today a gap exists between consumer health measurements and daily clinical practice, making this health data unusable for clinicians due to its unstructured, unverifiable and unreliable nature [11,12]. The development of devices for continuous measurement, such as smartwatches, further increases the amount of data that is generated, especially when combined with sensors using for instance photoplethysmography (PPG) technology, a photoelectric technique to record the change of blood volume in the vessels and thereby measuring heart rhythm or blood pressure [13]. To make use of its value, two developments are essential: structure and standardize health data and integrate it in electronic health records and make use of smart algorithms, possibly relying on machine learning, to automatically classify incoming data to prevent healthcare providers from being overwhelmed with irrelevant measurements [14].

Additionally, eHealth solutions will play a crucial role in addressing inequality in successful healthcare delivery, for instance illustrated by discrepancies in cardiovascular health outcomes in people with different socio-economic status (SES), also present in the Netherlands [15]. While interventions like remote monitoring could overcome geographical distances and provide permanent easy access to healthcare for patients with low SES, high eHealth literacy is associated with high SES and people from different age groups and diverse ethnic groups might encounter more difficulties in using digital resources [16,17]. To ensure that eHealth reduces rather than increases inequality in healthcare usage and health outcomes, special attention for the needs of vulnerable groups in society is key, especially because those are prone to having multiple chronic

disorders. Even in the most vulnerable and high risk populations, such as those living in slums in sub-Sahara Africa, community health programs have shown to reach those in need [18]. Recommendations rising from experience with those implementations have been extensively described and apply to eHealth implementation in those environments [19]. This leads to a third development for successful eHealth implementation: creative solutions to increase healthcare accessibility, for instance by enabling opportunities for blood pressure measurements in nontraditional healthcare settings such as barbershops, neighborhood houses and sports clubs are essential, preferably combined with personal digital health profiles [20]. Likewise, as a fourth essential development, interventions such as mobile applications should be designed with potential users with low eHealth literacy in mind, for instance making use of images, spoken text and immediate feedback [21]. Staff for instruction and intake of patients participating should (partly) consist of locals to increase factors like acceptability, ownership and participation [19].

While eHealth solutions for cardiovascular disease, when carefully designed, might be specifically beneficial for high-risk populations such as people with low SES, we should keep in mind that offering everything to everybody will hamper scalability and cost-effectiveness. For instance, the yield of arrhythmia detection in a random unselected population wearing an advanced smart watch is low, and even when diagnosed the necessity to follow-up and adjust therapy is uncertain when the finding classifies as low-risk [22]. The fifth essential development for eHealth programs is to carefully determine target groups based on changing risk classifications. An example is the assessment of the CHADSVASC score for patients with atrial fibrillation., who may need change of anticoagulation therapy during monitoring.

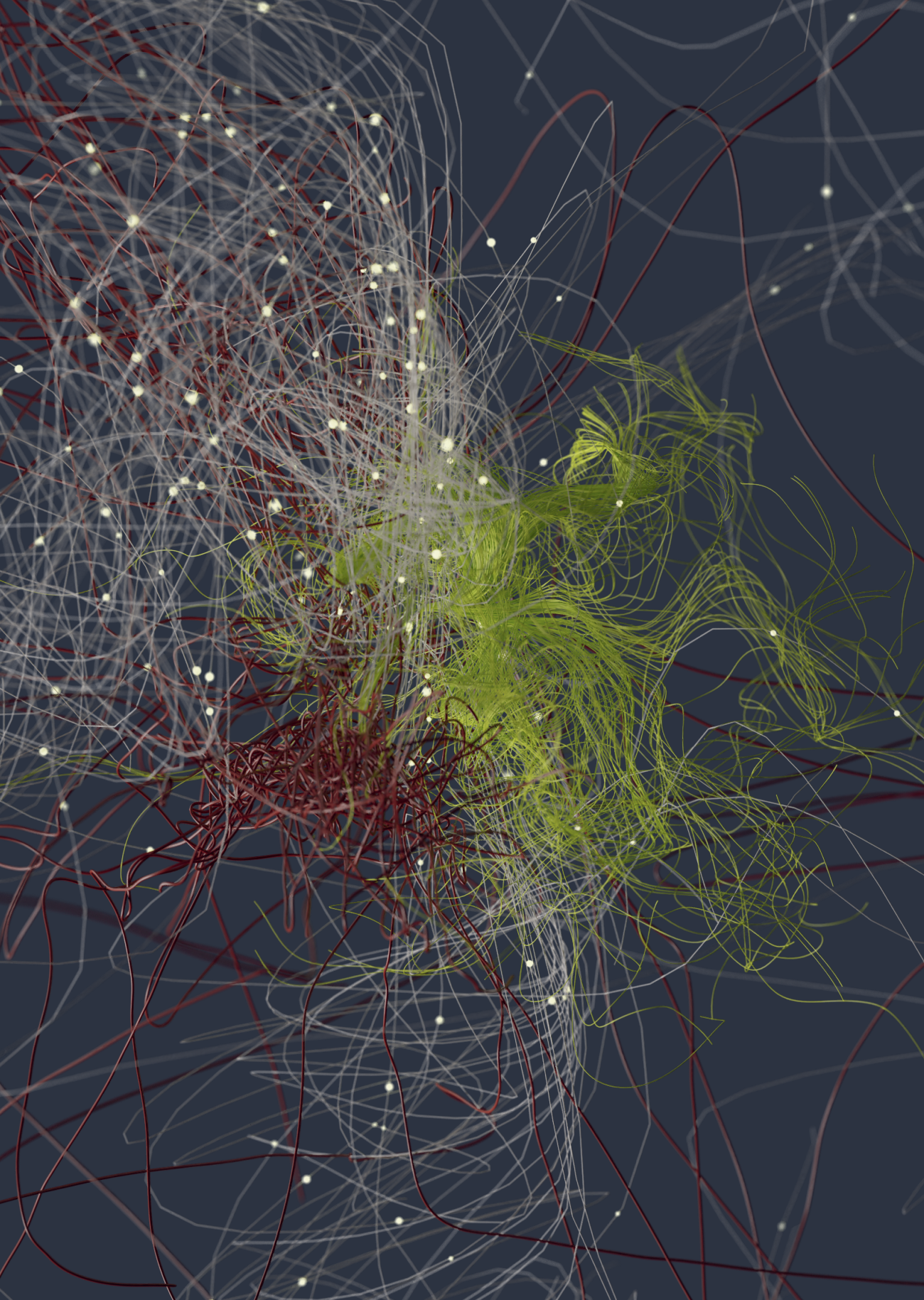
Even in high-risk groups with clear eHealth benefits, patient adherence has been a challenge, with numbers lost to follow-up reported to be high [23,24]. Limited user-friendliness of health measurement devices can be a reason for participants in eHealth programs to quit: classic blood pressure monitors for instance, are difficult to carry around and the compression of the vessels causes discomfort and is disruptive in daily life [25]. To overcome this, new technologies such as PPG have been highly anticipated, due to the continuous nature of its measurement and low burden for the user [13]. As health devices become increasingly focused on users outside the hospital rather than on clinical settings, new technology such as PPG-sensors decrease the burden to measure health and thereby improve patient adherence in eHealth. This demonstrates the sixth essential development: an evident trend towards seamless wearable health technology [13]. The continuation of this trend towards widely available, cheap, multifunctional implantable biosensors for real time patient monitoring is an imaginable next step [26].

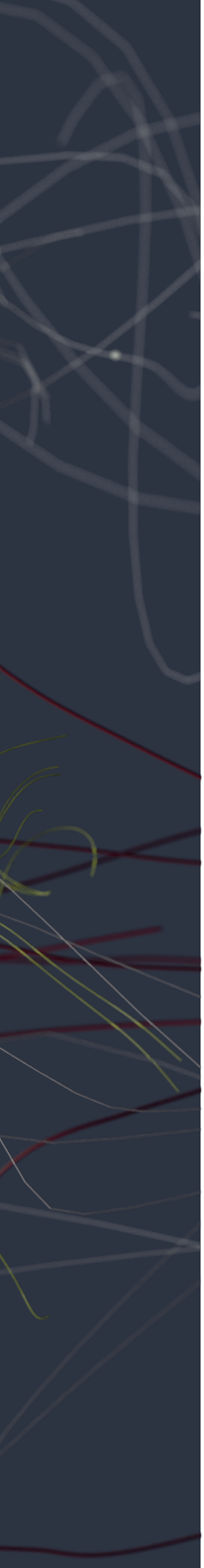
These six essential developments characterize the perspective of eHealth. Undoubtedly, the measurement, storage and transmission of health data will increase significantly following the digital revolution and widespread availability of cheap and functional consumer health devices. It is up to us, the scientific community, to guard this process and carefully guide the six essential developments. If we manage to do so, we increase the chance of a bright future, in which eHealth programs provide support rather than be a burden, save time rather than add workload and improve quality of healthcare. We can then aim for high quality healthcare, accessible independent of socio-economic status or literacy, with physicians having more time for arguably the most important part of healthcare that cannot be digitalized: personal and dedicated attention for the ones in need.

REFERENCES

1. Kotseva K, Wood D, Bacquer D De, Backer G De, Rydén L, Jennings C, Gyberg V, Amouyel P, Bruthans J, Castro Conde A, Cífková R, Deckers JW, Sutter J De, Dilic M, Dolzhenko M, Erglis A, Fras Z, Gaita D, Gotcheva N, Goudevenos J, Heuschmann P, Laucevicius A, Lehto S, Lovic D, Miličić D, Moore D, Nicolaides E, Oganov R, Pajak A, Pogosova N, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23: 636–648.
2. Wyatt JC, Sullivan F. ABC of health informatics: eHealth and the future: Promise or peril? *Br Med J* 2005; 331: 1391–1393.
3. Bashshur RL, Shannon G, Krupinski EA, Grigsby J. Sustaining and Realizing the Promise of Telemedicine. *Telemed e-Health* 2013; 19: 339–345.
4. Cavero-Redondo I, Saz-Lara A, Sequí-Dominguez I, Gómez-Guijarro MD, Ruiz-Grao MC, Martinez-Vizcaino V, Álvarez-Bueno C. Comparative effect of eHealth interventions on hypertension management-related outcomes: A network meta-analysis. *Int J Nurs Stud* 2021; 124: 104085.
5. Río-Lanza AB del, Suárez-Vázquez A, Suárez-Álvarez L, Iglesias-Argüelles V. Mobile health (mhealth): facilitators and barriers of the intention of use in patients with chronic illnesses. *J Commun Healthc* 2020; 13: 138–146.
6. Kolk MZH, Blok S, Wildt MCC De, Tjong FVY, Winter MM, Tulevski II, Born B-JH van den, Somsen GA. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal* 2021.
7. Selder JL, Breukel L, Blok S, Rossum AC van, Tulevski II, Allaart CP. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.
8. Blok S, Somsen GA, Tulevski II, Born B-J van den, Winter MM. Real-world experience with ehealth telemonitoring in patients with hypertension. *ESC 2019, Paris* Amsterdam; 2019.

9. Wierda E, Blok S, Somsen GA, Velde ET van der, Tulevski II, Stavrov B, Wildt MCC de, Born BJH van den, Breukel L, Mol BAJM de, Ploem MC, Winter MM. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of Hartwacht as a learning case. *BMJ Innov* 2020; 6: 170–176.
10. Cardiologie Centra Nederland. HartWacht. 2022. https://www.cardiologiecentra.nl/patient/meer-zorg/hartwacht/ (8 March 2022)
11. Kayser L, Kushniruk A, Osborne RH, Norgaard O, Turner P. Enhancing the effectiveness of consumer-focused health information technology systems through ehealth literacy: A framework for understanding users' needs. *JMIR Hum Factors* 2015; 2.
12. Lai AM, Hsueh PYS, Choi YK, Austin RR. Present and Future Trends in Consumer Health Informatics and Patient-Generated Health Data. *Yearb Med Inform* 2017; 26: 152–159.
13. Elgendi M, Fletcher R, Liang Y, Howard N, Lovell NH, Abbott D, Lim K, Ward R. The use of photoplethysmography for assessing hypertension. *npj Digit Med* 2019; 2: 1–11.
14. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018; 104: 1156–1164.
15. Blok S, Linden EL van der, Somsen GA, Tulevski II, Winter MM, Born B-JH van den. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2021; 28: 1579–1587.
16. Levin-Zamir D, Bertschi I. Media health literacy, Ehealth literacy, and the role of the social environment in context. *Int J Environ Res Public Health* 2018; 15: 1–12.
17. Car J, Tan WS, Huang Z, Sloot P, Franklin BD. eHealth in the future of medications management: Personalisation, monitoring and adherence. *BMC Med* 2017; 15: 1–9.
18. Vijver S van de, Oti SO, Gomez GB, Agyemang C, Egondi T, Charante EM van, Brewster LM, Hankins C, Tanovic Z, Ezeh A, Kyobutungi C, Stronks K. Impact evaluation of a community-based intervention for prevention of cardiovascular diseases in the slums of Nairobi: the SCALE-UP study. *Glob Health Action* 2016; 9: 30922.
19. Vijver S van de, Oti S, Oduor C, Ezeh A, Lange J, Agyemang C, Kyobutungi C. Challenges of health programmes in slums. *Lancet* 2015; 386: 2114–2116.
20. Victor RG, Lynch K, Li N, Blyler C, Muhammad E, Handler J, Brettler J, Rashid M, Hsu B, Foxx-Drew D, Moy N, Reid AE, Elashoff RM. A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops. *N Engl J Med* 2018; 378: 1291–1301.
21. Pharos. eHealth development only successful with target groups involvement. Utrecht; 2016.
22. Perez M V., Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, Hills MT, Desai S, Granger CB, Desai M, Turakhia MP. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; 381: 1909–1917.
23. McMahon J, Thompson DR, Pascoe MC, Brazil K, Ski CF. eHealth interventions for reducing cardiovascular disease risk in men: A systematic review and meta-analysis. *Prev Med (Baltim)* 2021; 145: 106402.
24. Sieverink F, Kelders SM, Gemert-Pijnen V. Clarifying the concept of adherence to ehealth technology: Systematic review on when usage becomes adherence. *J Med Internet Res* 2017; 19: 1–16.
25. Liu J, Yan BP, Zhang Y, Ding X, Su P, Zhao N. Multi-Wavelength Photoplethysmography Wearable Electronics. *IEEE Trans Biomed Eng* 2019; 66: 1514–1525.
26. Rodrigues D, Barbosa AI, Rebelo R, Kwon IK, Reis RL, Correlo VM. Skin-integrated wearable systems and implantable biosensors: A comprehensive review. *Biosensors* 2020; 10.





Chapter 11

Summary

SUMMARY

In this thesis we investigated different aspects of eHealth for hypertension and cardiovascular disease, with a focus on remote monitoring programs for chronic care. We used the Dutch HartWacht program for patients with hypertension, cardiac arrhythmias and heart failure as an example that has already been implemented in routine clinical care. We focused on hypertension and identified areas that are attractive for future implementation because of poor hypertension control. With that aim, in **chapter 2** we used data from the Healthy Life in an Urban Setting (HELIUS) study and examined the association between socio-economic status (SES) and the prevalence, awareness, treatment and control of hypertension in different ethnic groups. As described in earlier research, we observed an association between a lower SES and increased prevalence of hypertension in all ethnic groups. However, we found no differences in hypertension awareness between individuals with lower and higher SES, which may point towards a relatively high accessibility of the Dutch healthcare system with universal coverage. Notably, individuals with higher SES used less medication, but more often had their blood pressure controlled compared to those with lower SES, and these associations were partly impacted by ethnicity. Our analysis demonstrates that across ethnic groups, a gap exists between those that receive treatment and those that have their blood pressure controlled, especially in individuals with a low SES. In facing this challenge of delivering healthcare to this high-risk population, eHealth programs can play an important role. In line with this, such programs can potentially bridge an even bigger health gap by serving previously unreached populations in low- and middle income countries.

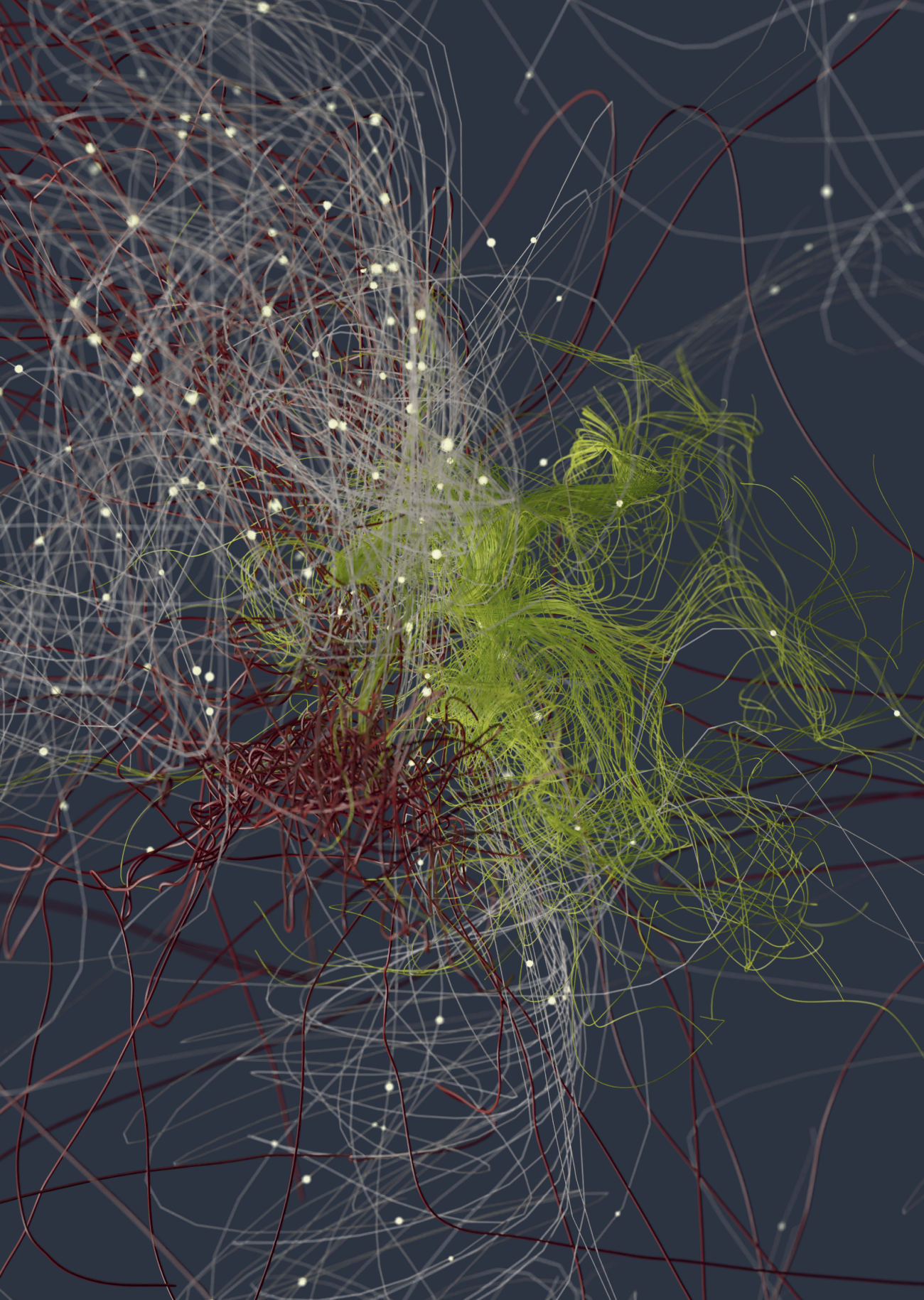
In the following chapters we present economical, legal and technical challenges that accompany eHealth implementation, in each chapter followed by potential solutions and opportunities. In **chapter 3** we continue by evaluating whether eHealth can be a cost-effective method of healthcare delivery in patients with hypertension. We systematically searched literature for evidence on remote monitoring programs and performed a meta-analysis of the gathered data. We found the studies on this subject to be heterogeneous, with varying results on costs and effectiveness. Nevertheless, we distilled three critical factors for cost-effective remote monitoring that successful programs have in common. First, in order to be effective an eHealth initiative should be high in intensity, actively responding to measurements with personalized feedback. Second, to increase efficiency and reduce costs per patient, scaling up is essential. Third, to lower overall costs the remote monitoring intervention should be replacing part of the usual care process, rather than be added to it. Initiatives that combine these three

factors have shown to be cost-effective. In **chapter 4** we evaluate the data protection measurements that such large-scale eHealth interventions should apply in order to be compliant with applicable rules and laws, specifically the General Data Protection Regulation (GDPR) as applied in the European Union. We provide a framework for seven elements of eHealth and describe the measures that were taken to ensure that the Dutch HartWacht program is fully compliant. In **chapter 5** we investigate the feasibility of a novel technique, photoplethysmography (PPG), to detect heartbeats and more specifically, heart rate and RR-intervals. We studied the accuracy of a PPG sensor integrated in a bracelet compared to a 12-lead ECG as a golden standard, in a population at risk for cardiovascular disease. Our study demonstrates that, specifically when applying a signal qualifier that supports automated classification of the PPG-signal quality, the sensor is highly accurate. Due to their non-intrusive and convenient nature, wearable devices like these have great potential for high volume accessible long-term monitoring at-risk cardiac patients. In **chapter 6** we address the pitfall of eHealth solutions in gathering large amounts of data that are presented to healthcare providers, leading to increased workload and risk of alarm fatigue. This hampers upscaling and additionally alarm fatigue can cause apathy and desensitization of physicians and harm patient safety because it makes real events less likely to be acted on. Our analysis, using realworld data from the HartWacht program, shows a potential decrease in workload of almost one third, by applying relatively simple rules for automized classification of incoming data. It additionally shows that unactionable notifications can be diminished, thereby reducing the risk of alarm fatigue.

In the following chapters we zoom in on the patients participating in eHealth programs. In **chapter 7** we evaluate the impact on quality of life of patients participating in the HartWacht program for cardiac arrhythmias. Validated questionnaires were used to gather data on generic Health Related Quality of Life (HRQoL), disease-specific HRQoL, sense of safety, physical limitations and self-management. We found no significant change in HRQoL and sense of safety during follow-up, but a significant improvement in the perceived physical limitations. Notably, the level of self-management declined significantly during follow-up, possibly caused by participants being more involved with their disorder and therefore having more questions that, if remained unanswered, may cause additional concerns and the feeling of losing control. This shows the relevance of incorporating patient feedback and patient education. In general, compared to the usual care group, in disease-specific HRQoL, sense of safety and physical limitations HartWacht showed equivalence or increase. This equivalence in patient-reported outcomes to usual care advocates for a broader implementation of

such eHealth programs since this improves accessibility and lower healthcare costs. In **chapter 8**, we provide the rationale, design and cohort profile of the Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (EMPATHY) trial in which we investigate the effectiveness of the HartWacht program. In preparation of this trial, we evaluated the feasibility of the program and compared patients that successfully achieved blood pressure control during participation with those who did not in order to identify patient characteristics that contribute to success. The feasibility was demonstrated by a significant average decrease of blood pressure at follow up in these hypertensive patients. Overall, almost two third achieved blood pressure control at three- and six-months follow-up. Because no differences were found in phenotypical characteristics between patients whose blood pressure decreased, and in patients whose blood pressure remained unchanged we applied broad inclusion criteria in the EMPATHY trial. For that study, we compare HartWacht with usual care, primarily on blood pressure measured with a 24-hour blood pressure, and secondarily on renal function as measured with albumin creatinine ratio.

We conclude in **chapter 9** with an evaluation of the impact of the COVID-19 pandemic on the uptake of eHealth in primary care in the Netherlands. During the pandemic, the use of an eHealth platform for remote hypertension management increased significantly. We demonstrate that the pandemic increased urgency for remote care because physical contact was necessarily limited. At the same time, even in such situations introduction of innovations like eHealth are not successful without structural support. In our study we show that the combination of an increased sense of urgency with factors like availability of time of the healthcare provider and practical support for the implementation on the patient side are crucial for the uptake of a digital service. Hopefully, we don't need new outbreaks to continue this acceleration of innovations.



Appendices

Nederlandse samenvatting en discussie
Authors and affiliations
List of publications
Portfolio
Dankwoord
About the author (curriculum vitae)

NEDERLANDSE SAMENVATTING EN DISCUSSIE

In dit proefschrift belichten we verschillende aspecten van eHealth programma's voor hypertensie en cardiovasculaire aandoeningen, waarbij de focus ligt op monitoring op afstand voor chronische zorg. We hebben het Nederlandse HartWacht programma, voor patiënten met hypertensie, hartritmestoornissen en chronisch hartfalen, gebruikt als een voorbeeld dat is geïmplementeerd in de dagelijkse poliklinische praktijk.

Specifiek hebben we naar hypertensie gekeken, waarbij we in eerste instantie hebben onderzocht op welke vlakken bloeddrukcontrole voor verbetering vatbaar is, en daarmee een aantrekkelijk toepassingsgebied voor eHealth. Met dat doel hebben we voor **hoofdstuk 2** data gebruikt uit de Healthy Life in an Urban Setting (HELIUS) studie, en de associatie tussen socio-economische status (SES) en de prevalentie, het bewust zijn, behandeling en controle van hypertensie onderzocht in verschillende etnische groepen. Zoals al eerder aangetoond, zagen we een associatie tussen lagere SES en toenemende prevalentie van hypertensie in alle etnische groepen. We zagen echter geen verschillen in de aantallen individuen die zich bewust waren van hun hypertensie, iets dat kan wijzen op de goede toegankelijkheid van het Nederlandse zorgsysteem met dekking vanuit het verzekerde basispakket. We zagen opmerkelijk genoeg ook dat individuen met een hogere SES minder bloeddrukmedicatie gebruikten, maar de bloeddruk toch vaker onder controle hadden vergeleken met individuen met een lagere SES, en dat deze associaties beïnvloed werden door etniciteit. Onze analyse laat zien dat er bij alle etnische groepen een kloof bestaat tussen individuen die therapie ontvangen voor hun bloeddruk en zij die daadwerkelijk bloeddrukcontrole bereiken, voornamelijk bij hen met een lage SES. Bij deze uitdaging, om zorg effectief aan te bieden aan specifiek deze hoog-risico populatie, kunnen eHealth programma's een belangrijke rol spelen. In lijn hiermee kunnen dit soort programma's wellicht een nog grotere kloof dichten, en zelfs moeilijk bereikbare populaties bedienen in landen met middel- en laag inkomen.

In de hierop volgende hoofdstukken beschrijven we economische, juridische en technische uitdagingen rondom eHealth implementaties, in elk hoofdstuk gevolgd door potentiële oplossingen en mogelijkheden. In **hoofdstuk 3** evalueren we of eHealth een kosteneffectieve methode kan zijn voor zorg voor patiënten met hypertensie. Met dat doel doorzochten we systematisch literatuur op beschikbaar bewijs en voerden een meta-analyse uit op de verzamelde data. De gevonden studies waren heterogeen in methodiek en uitkomsten, met variatie op het gebied van kosten en effectiviteit. Desalniettemin konden we drie kritieke succesfactoren voor kosten-effectieve eHealth

identificeren die studies met succesvolle programma's met elkaar gemeen hadden. Ten eerste, om effectief te zijn dient een interventie intensief te zijn, wat inhoudt dat er actief gereageerd wordt, met persoonlijke feedback, op metingen die patiënten uitvoeren. Ten tweede, om efficiëntie te verhogen en kosten per patiënt te reduceren, is opschaling essentieel. Tenslotte, om totale kosten te beperken, zullen eHealth programma's ten minste gedeeltelijk reguliere zorg moeten vervangen, in plaats van als toevoeging ingezet te worden. Initiatieven die deze drie factoren combineren in hun opzet laten zien kosteneffectief te kunnen zijn. In **hoofdstuk 4** evalueren we vervolgens de maatregelen rondom databeveiliging waarover dergelijke eHealth programma's dienen te beschikken, teneinde compliant te zijn met wet- en regelgeving en specifiek de *General Data Protection Regulation* (GDPR) zoals deze wordt toegepast in de Europese Unie. We presenteren een raamwerk met zeven elementen van eHealth en beschrijven de maatregelen die zijn genomen binnen het HartWacht programma om compliantie te waarborgen. Voor **hoofdstuk 5** hebben we naar de toepasbaarheid gekeken van een nieuwe techniek, fotoplethysmografie (photoplethysmography (PPG)), om hartslagen waar te nemen en meer specifiek om hartslag en RR-intervallen te detecteren. We vergeleken de accuraatheid van de PPG-sensor, geïntegreerd in een polsbandje, met de gouden standaard, een 12-kanaals ECG, in een populatie met hoog risico op cardiovasculaire aandoeningen. In dit hoofdstuk laten we zien dat deze methodiek zeer nauwkeurig is, voornamelijk in combinatie met automatische classificatie van signaalkwaliteit. Dankzij de non-invasieve aard en het hoge draagcomfort in vergelijking met bijvoorbeeld traditionele holtertechniek, hebben dergelijke sensoren grote potentie voor toegankelijke lange termijn monitoring op grote schaal. In **hoofdstuk 6** adresseren we de uitdaging van eHealth programma's waarin zeer veel data wordt verzameld die door zorgmedewerkers moet worden beoordeeld, waardoor een toename van werkdruk dreigt en mogelijke opschaling wordt tegengehouden. De grote hoeveelheden notificaties kunnen daarnaast leiden tot alarmmoeheid, waardoor risico op onjuist of niet handelen toeneemt en daarmee patiëntveiligheid afneemt. Onze analyse, waarbij we gebruik maken van data uit het HartWacht programma, laat zien dat door relatief eenvoudige regels toe te passen voor geautomatiseerde afhandeling van metingen, de werkdruk met een derde kan afnemen. Daarnaast laten we zien dat met automatische classificatiesystemen onnodige notificaties kunnen worden voorkomen, waarmee het risico op alarmmoeheid daalt.

In de daaropvolgende hoofdstukken kijken we specifieker naar de patiënten die deelnemen aan eHealth programma's. In **hoofdstuk 7** evalueren we de impact van deelname aan het HartWacht programma voor hartritmestoornissen op de kwaliteit van

leven van patiënten. We hebben daarvoor gebruik gemaakt van gevalideerde vragenlijsten om data te verzamelen. We vonden geen significante veranderingen in kwaliteit van leven en gevoel van veiligheid bij follow-up, maar wel een verbetering van ervaren fysieke beperkingen. Het gevoel van zelfmanagement verminderde tijdens deelname, mogelijkerwijs veroorzaakt doordat patiënten meer betrokken zijn bij hun aandoening en daardoor ook meer vragen hebben die, indien deze onbeantwoord blijven, zorgen voor een gevoel van onrust en controleverlies. Dit duidt op het belang van educatie en feedback voor deelnemende patiënten. In het algemeen was kwaliteit van leven van HartWacht deelnemers, vergeleken patiënten die reguliere zorg ontvingen, minimaal equivalent en in specifieke gevallen beter. In **hoofdstuk 8** beschrijven we de rationale, het ontwerp en het cohort profiel van de Effectiveness of home-Monitoring of blood pressure in PAtients with difficult to Treat HYpertension (*EMPATHY*) trial, waarin de effectiviteit van het HartWacht programma onderzoeken. In voorbereiding op deze trial hebben we de toepasbaarheid van het programma geëvalueerd, en patienten die succesvol waren en bloeddrukcontrole bereikten tijdens deelname vergeleken met hen die niet succesvol waren, om factoren te identificeren die succes kunnen voorspellen. We laten zien dat bloeddruk tijdens deelname significant daalde en dat ongeveer twee derde van de deelnemers de bloeddruk onder controle kreeg, maar we vonden geen verschillen in fenotypische karakteristieken tussen deze patiënten en hen die geen controle bereikten. We hielden daardoor brede inclusiecriteria aan voor de EMPATHY-trial. In die studie vergelijken we HartWacht-deelnemers met patiënten die reguliere zorg ontvangen middels een 24-uurs bloeddrukmeting en bepaling van de nierfunctie.

We eindigen in **hoofdstuk 9** met een evaluatie van de impact van de COVID-19 pandemie op de implementatie van eHealth in de eerstelijns zorg in Nederland. Gedurende deze pandemie nam het gebruik van digitale zorg significant toe in de onderzochte huisartsenpraktijken. We laten in dit hoofdstuk zien dat de pandemie een urgentie creëerde voor zorg op afstand, omdat fysieke contacten noodzakelijkerwijs tot het minimum beperkt werden. Tegelijkertijd is, zelfs in zulke tijden, de implementatie van dergelijke innovaties niet succesvol zonder structurele support. In onze studie beschrijven we dat de combinatie van toegenomen urgentie met andere factoren zoals beschikbaarheid van tijd van de zorgverlener en praktische ondersteuning aan de kant van de deelnemende patiënt cruciaal is voor de invoer van eHealth. Hopelijk hebben we geen nieuwe pandemieën nodig om deze accelaratie van eHealth implementatie te continueren.

De belofte van eHealth

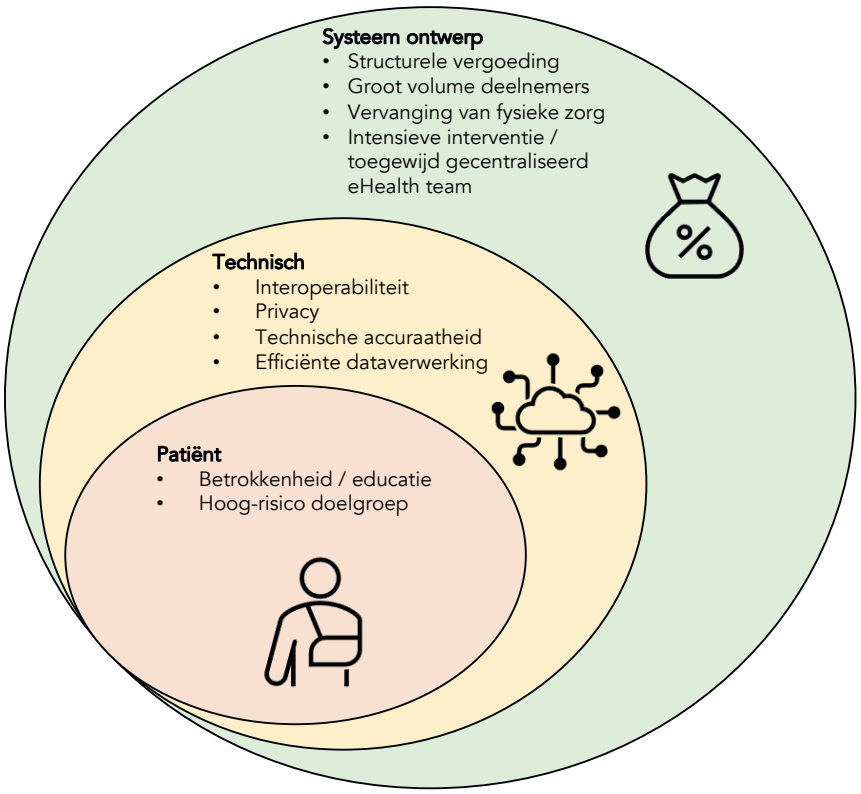
Teleurstellende lange termijneffecten van behandelingen voor cardiovasculaire aandoeningen worden niet veroorzaakt door een gebrek aan therapeutische mogelijkheden. Effectieve en goedkope behandeling is immers ruimschoots voorhanden. Voornamelijk gaat het om beperkte executie in de klinische praktijk, waaronder bijvoorbeeld inertie van de arts en beperkte therapietrouw van patiënten vallen [1]. De belangrijkste uitdaging van onze vergrijzende maatschappij, met toenemende aantallen chronische aandoeningen, is hoe op effectieve wijze bewezen therapieën aan te bieden aan diegenen die daar baat bij hebben. In de afgelopen jaren is eHealth vaak genoemd als strategie om deze uitdaging het hoofd te bieden: patiënten zouden goed geïnformeerde zorgdrager van de eigen gezondheid worden en het beroep van arts zou veranderen naar zorgmanager op afstand [2]. Bovendien zouden zulke initiatieven leiden tot verbeterde toegankelijkheid, hogere kwaliteit en beheersbare kosten van onze gezondheidszorg [3]. Maar terwijl bewijs over bijvoorbeeld de effectiviteit van monitoring op afstand voor hypertensie en de voordelen van eHealth zich opstapelde, zeker tijdens de COVID pandemie, heeft eHealth deze verwachtingen slechts in zeer beperkte mate kunnen waarmaken, omdat implementatie in de klinische praktijk achterbleef [4,5].

Huidige succesfactoren

Het Nederlandse HartWacht programma, gelanceerd in 2016, is een voorbeeld van een eHealth initiatief dat succesvol is geïntegreerd en over de loop van de jaren is opgeschaald [6–9]. Momenteel hebben ongeveer 7.000 patiënten van 13 poliklinieken verspreid over Nederland als onderdeel van hun reguliere zorg deelgenomen aan dit programma [10]. Generaliseerbare succesfactoren die dit programma karakteriseren, zoals beschreven in dit proefschrift, kunnen worden onderverdeeld in drie categorieën: i) aspecten van het systeem waarin eHealth opereert, ii) technische vereisten van de eHealth infrastructuur en iii) patiënt-gerelateerde aspecten (zie Figuur 1).

Toekomstperspectieven

De doorlopende ontwikkeling van steeds geavanceerdere gebruiksvriendelijke digitale meetinstrumenten voor consumenten leidt ertoe dat gezondheidsmetingen in toenemende mate onafhankelijk van artsen of zorgverleners worden uitgevoerd. Er bestaat echter een kloof tussen deze metingen, uitgevoerd door de consument zelf, en de dagelijkse klinische praktijk, waardoor de data vaak onbruikbaar zijn voor clinici omdat deze ongestructureerd, onverifieerbaar en onbetrouwbaar zijn [11,12]. De ontwikkeling van apparaten voor continue metingen, zoals slimme horloges met fotoplethysmogra-



Figuur 1: Succesfactoren voor schaalbare eHealth oplossingen.

fie (PPG) technologie, leidt ertoe dat de hoeveelheid data alleen nog maar toeneemt. Om hier toch waarde uit te creëren zijn twee ontwikkelingen essentieel: ten eerste het structureren en standaardiseren van gezondheidsdata en deze integreren en beschikbaar maken in elektronische patiëntendossiers, en ten tweede het gebruik maken van slimme algoritmes, indien van toepassing ondersteund door machine learning, om automatisch binnenkomende data te classificeren en ondervangen en zo te voorkomen dat zorgverleners overspoeld worden door irrelevante metingen [13].

eHealth toepassingen zullen daarnaast een cruciale rol spelen in het adresseren van de ongelijkheid in de toegankelijkheid en bereikbaarheid van zorg, die bijvoorbeeld wordt geïllustreerd door de discrepanties in cardiovasculaire gezondheidsuitkomsten in individuen met verschillende Socio-Economische Status (SES), ook in Nederland [14]. Terwijl interventies zoals monitoring op afstand geografische afstand kunnen overbruggen en zorg permanent en eenvoudig toegankelijk kunnen maken, is hogere

eHealth-vaardigheid geassocieerd met hogere SES en kunnen mensen uit verschillende leeftijdsgroepen en met diverse etnische achtergronden moeilijkheden ervaren in het gebruik van digitale middelen [15,16]. Om te zorgen dat eHealth ongelijkheid vermindert in plaats van laat toenemen is het essentieel dat er aandacht is voor de specifieke behoeften van kwetsbare groepen in onze maatschappij, zeker omdat sommige van deze groepen extra risico lopen op multipele chronische aandoeningen. Zelfs in de meest kwetsbare en hoog-risico populaties, zoals bewoners van sloppenwijken in sub-Sahara Afrika, kunnen programma's met focus op gezondheid diegenen die het nodig hebben bereiken [17]. Aanbevelingen voortkomend uit ervaringen met zulke implementaties zijn uitgebreid beschreven en zijn ook van toepassing op de implementatie van eHealth in zulke omgevingen [18]. Dit leidt tot een derde essentiële ontwikkeling voor eHealth: creatieve oplossingen om toegankelijkheid van zorg te vergroten, bijvoorbeeld door het mogelijk maken van bloeddrukmetingen in niet-traditionele zorgsettings zoals kappers, buurthuizen en sportclubs, gecombineerd met digitale persoonlijke profielen waarin metingen worden opgeslagen en verwerkt [19]. Tevens, als vierde essentiële ontwikkeling, moet bij de ontwikkeling van eHealth applicaties de eindgebruiker met verminderde geletterdheid en digitale vaardigheden in gedachten worden gehouden, waarbij middelen als afbeeldingen, gesproken woord en directe feedback een uitkomst kunnen zijn [20]. Personeel voor instructie en intake van aan eHealth deelnemende programma's moet bestaan uit mensen representatief voor de doelgroep, om factoren zoals acceptatie, eigenaarschap en participatie te bevorderen [18].

eHealth oplossingen kunnen dus, indien zorgvuldig ontworpen en geïmplementeerd, met name toegevoegde waarde hebben voor hoog-risico populaties zoals mensen met lagere SES. Tegelijkertijd weten we dat alles aan iedereen aanbieden kosteneffectiviteit en schaalbaarheid belemmert. De opbrengst, bijvoorbeeld, van monitoring voor hartritmestoornissen met een geavanceerde smartwatch in een niet-geselecteerde, willekeurige populatie is laag [21]. En zelfs als in deze groep een afwijking wordt geconstateerd is de noodzaak van opvolging en therapie niet altijd duidelijk, als het bijvoorbeeld gaat om een laag-risico aandoening bij een laag-risico individu. De vijfde essentiële ontwikkeling voor eHealth programma's, zoals continue monitoring van hartritme, is het zorgvuldig vaststellen van doelgroepen, gebaseerd op risicoclassificaties zoals de CHADSVASC-score, en de noodzaak van follow-up acties, zoals anticoagulatie, bij afwijkende metingen.

Zelfs in deze hoog-risico groepen met duidelijke voordelen van eHealth is de adherentie van patiënten een uitdaging. De aantallen patiënten die afhaken tijdens het programma zijn vaak hoog [22,23]. Beperkte gebruiksvriendelijkheid van meetapparatuur

kan een reden zijn voor deelnemers om te stoppen met meten. Klassieke bloeddrukmeters nodigen bijvoorbeeld niet uit ze overal mee naartoe te nemen, en daarnaast is de compressie van bloedvaten oncomfortabel en is het doen van een meting een hinderlijke onderbreking van dagelijkse bezigheden [24]. Op dit gebied kunnen we veel verwachten van nieuwe technieken zoals PPG, omdat deze het mogelijk maken continu te meten zonder last voor de gebruiker [25]. Doordat consumentenelektronica in toenemende mate gefocust zijn op gebruikers buiten de muren van het ziekenhuis, in plaats van op klinische settings, zal de last voor gebruikers om gezondheidsmetingen uit te voeren verder verminderen en daarbij adherentie van patiënten binnen eHealth programma's doen toenemen. Hierbij zien we als zesde essentiële ontwikkeling een duidelijke trend richting draagbare apparatuur. De continuering van deze trend naar ruim beschikbare, goedkope, multifunctionele implanteerbare biosensoren voor real time monitoring van patiënten is voorstelbaar [26].

We kunnen de toekomstige perspectieven van eHealth samenvatten in deze zes essentiële ontwikkelingen. Het leidt geen twijfel dat het meten, opslaan en verzenden van gezondheidsdata significant zal toenemen, volgend op de digitale revolutie en ruime beschikbaarheid van goedkope en functionele consumentenelektronica. Het is aan ons, de wetenschappelijke gemeenschap, dit proces te bewaken en een gids te zijn voor de zes essentiële ontwikkelen van eHealth. Als we daarin slagen vergroten we de kans op een rooskleurige toekomst, waarin eHealth programma's een steun zijn in plaats van een last, tijd besparen in plaats van tijd kosten en kwaliteit van zorg doen toenemen. We kunnen dan streven naar hoogkwalitatieve zorg, toegankelijk onafhankelijk van socio-economische status of geletterdheid, waarin artsen meer tijd hebben voor wat waarschijnlijk het belangrijkste onderdeel is van onze zorg en wat niet kan worden gedigitaliseerd: persoonlijke en toegewijde aandacht voor hen die dat nodig hebben.

Referenties

1. Kotseva K, Wood D, Bacquer D De, Backer G De, Rydén L, Jennings C, Gyberg V, Amouyel P, Bruthans J, Castro Conde A, Cífková R, Deckers JW, Sutter J De, Dilic M, Dolzhenko M, Erglis A, Fras Z, Gaita D, Gotcheva N, Goudevenos J, Heuschmann P, Laucevicius A, Lehto S, Lovic D, Miličić D, Moore D, Nicolaides E, Oganov R, Pajak A, Pogosova N, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23: 636–648.
2. Wyatt JC, Sullivan F. ABC of health informatics: eHealth and the future: Promise or peril? *Br Med J* 2005; 331: 1391–1393.
3. Bashshur RL, Shannon G, Krupinski EA, Grigsby J. Sustaining and Realizing the Promise of Telemedicine. *Telemed e-Health* 2013; 19: 339–345.

4. Cavero-Redondo I, Saz-Lara A, Sequí-Dominguez I, Gómez-Guijarro MD, Ruiz-Grao MC, Martinez-Vizcaino V, Álvarez-Bueno C. Comparative effect of eHealth interventions on hypertension management-related outcomes: A network meta-analysis. *Int J Nurs Stud* 2021; 124: 104085.
5. Río-Lanza AB del, Suárez-Vázquez A, Suárez-Álvarez L, Iglesias-Argüelles V. Mobile health (mhealth): facilitators and barriers of the intention of use in patients with chronic illnesses. *J Commun Healthc* 2020; 13: 138–146.
6. Kolk MZH, Blok S, Wildt MCC De, Tjong FVY, Winter MM, Tulevski II, Born B-JH van den, Somsen GA. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal* 2021.
7. Selder JL, Breukel L, Blok S, Rossum AC van, Tulevski II, Allaart CP. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.
8. Blok S, Somsen GA, Tulevski II, Born B-J van den, Winter MM. Real-world experience with ehealth telemonitoring in patients with hypertension. *ESC 2019, Paris* Amsterdam; 2019.
9. Wierda E, Blok S, Somsen GA, Velde ET van der, Tulevski II, Stavrov B, Wildt MCC de, Born BJH van den, Breukel L, Mol BAJM de, Ploem MC, Winter MM. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of Hartwacht as a learning case. *BMJ Innov* 2020; 6: 170–176.
10. Cardiologie Centra Nederland. HartWacht. 2022. https://www.cardiologiecentra.nl/patient/meer-zorg/hartwacht/ (8 March 2022)
11. Kayser L, Kushniruk A, Osborne RH, Norgaard O, Turner P. Enhancing the effectiveness of consumer-focused health information technology systems through ehealth literacy: A framework for understanding users' needs. *JMIR Hum Factors* 2015; 2.
12. Lai AM, Hsueh PYS, Choi YK, Austin RR. Present and Future Trends in Consumer Health Informatics and Patient-Generated Health Data. *Yearb Med Inform* 2017; 26: 152–159.
13. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018; 104: 1156–1164.
14. Blok S, Linden EL van der, Somsen GA, Tulevski II, Winter MM, Born B-JH van den. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2021; 28: 1579–1587.
15. Levin-Zamir D, Bertschi I. Media health literacy, Ehealth literacy, and the role of the social environment in context. *Int J Environ Res Public Health* 2018; 15: 1–12.
16. Car J, Tan WS, Huang Z, Sloot P, Franklin BD. eHealth in the future of medications management: Personalisation, monitoring and adherence. *BMC Med* 2017; 15: 1–9.
17. Vijver S van de, Oti SO, Gomez GB, Agyemang C, Egondi T, Charante EM van, Brewster LM, Hankins C, Tanovic Z, Ezeh A, Kyobutungi C, Stronks K. Impact evaluation of a community-based intervention for prevention of cardiovascular diseases in the slums of Nairobi: the SCALE-UP study. *Glob Health Action* 2016; 9: 30922.
18. Vijver S van de, Oti S, Oduor C, Ezeh A, Lange J, Agyemang C, Kyobutungi C. Challenges of health programmes in slums. *Lancet* 2015; 386: 2114–2116.
19. Victor RG, Lynch K, Li N, Blyler C, Muhammad E, Handler J, Brettler J, Rashid M, Hsu B, Foxx-Drew D, Moy N, Reid AE, Elashoff RM. A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops. *N Engl J Med* 2018; 378: 1291–1301.
20. Pharos. eHealth development only successful with target groups involvement. Utrecht; 2016.

21. Perez M V., Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, Hills MT, Desai S, Granger CB, Desai M, Turakhia MP. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; 381: 1909–1917.
22. McMahon J, Thompson DR, Pascoe MC, Brazil K, Ski CF. eHealth interventions for reducing cardiovascular disease risk in men: A systematic review and meta-analysis. *Prev Med (Baltim)* 2021; 145: 106402.
23. Sieverink F, Kelders SM, Gemert-Pijnen V. Clarifying the concept of adherence to ehealth technology: Systematic review on when usage becomes adherence. *J Med Internet Res* 2017; 19: 1–16.
24. Liu J, Yan BP, Zhang Y, Ding X, Su P, Zhao N. Multi-Wavelength Photoplethysmography Wearable Electronics. *IEEE Trans Biomed Eng* 2019; 66: 1514–1525.
25. Elgendi M, Fletcher R, Liang Y, Howard N, Lovell NH, Abbott D, Lim K, Ward R. The use of photoplethysmography for assessing hypertension. *npj Digit Med* 2019; 2: 1–11.
26. Rodrigues D, Barbosa AI, Rebelo R, Kwon IK, Reis RL, Correlo VM. Skin-integrated wearable systems and implantable biosensors: A comprehensive review. Biosensors 2020; 10.

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LIST OF PUBLICATIONS

Blok S, Haggenburg S, Collard D, Linden EL Van Der, Galenkamp H, Charante EPM Van, Agyemang C, Born B-JH Van Den. The association between socioeconomic status and prevalence, awareness, treatment and control of hypertension in different ethnic groups: the Healthy Life in an Urban Setting study. *J Hypertens* 2022; 40: 897–907.

Blok S, Linden EL van der, Somsen GA, Tulevski II, Winter MM, Born B-JH van den. Success factors in high-effect, low-cost eHealth programs for patients with hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2021; 28: 1579–1587.

Wierda E, **Blok S**, Somsen GA, Velde ET van der, Tulevski II, Stavrov B, Wildt MCC de, Born BJH van den, Breukel L, Mol BAJM de, Ploem MC, Winter MM. Protecting patient privacy in digital health technology: the Dutch m-Health infrastructure of HartWacht as a learning case. *BMJ Innov* 2020; 6: 170–176.

Blok S, Piek MA, Tulevski II, Somsen GA, Winter MM. The accuracy of heartbeat detection using photoplethysmography technology in cardiac patients. *J Electrocardiol* 2021; 67: 148–157.

Kolk MZH, **Blok S**, Wildt MCC De, Tjong FVY, Winter MM, Tulevski II, Born B-JH van den, Somsen GA. Patient-reported outcomes in symptom-driven remote arrhythmia monitoring: evaluation of the Dutch HartWacht-telemonitoring programme. *Eur Hear J - Digit Heal* 2021.

Selder JL, Breukel L, **Blok S**, Rossum AC van, Tulevski II, Allaart CP. A mobile one-lead ECG device incorporated in a symptom-driven remote arrhythmia monitoring program. The first 5,982 Hartwacht ECGs. *Netherlands Hear J* 2019; 27: 38–45.

Kauw D, Koole MAC, Winter MM, Dohmen DAJ, Tulevski II, **Blok S**, Somsen GA, Schijven MP, Vriend JWJ, Robbers-Visser D, Mulder BJM, Bouma BJ, Schuuring MJ. Advantages of mobile health in the management of adult patients with congenital heart disease. *Int J Med Inform* 2019; 132: 104011.

Blok S, Somsen GA, Bevers M, Van de Vijver S. Medisch Contact – 15th of June 2021 (original article in Dutch). Available from: https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/corona-geeft-e-healthinnovaties-wind-in-de-rug.htm

PORTFOLIO

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1. PhD training		
Presentations		
European Congress on eCardiology and eHealth (ESC, Berlin, Germany)		2017
European Congress on eCardiology and eHealth (ESC, Moscow, Russia)		2018
New information technology and changing physician-patient relationship congress (KNMG, Amsterdam, the Netherlands)		2018
European Society of Cardiology congress (ESC, Paris, France)		2019
Value Based Healthcare congress (VBHC, Amerongen, the Netherlands)		2019
Dutch Hypertension Congres (NHV, Amersfoort, the Netherlands)		2019
European Society of Cardiology digital summit (ESC, Tallin, Estonia)		2019
Value Based Healthcare congress (VBHC, Amerongen, the Netherlands)		2020
European Society of Cardiology congress (ESC, Amsterdam, the Netherlands)		2021

2. Teaching		
Supervising		
Master Thesis:	Sanna Verhage	2019
Bachelor Thesis:	Tijmen Beemster	2019
Master Thesis:	Carine Smit	2020
Master Thesis:	Floris Korten	2020
Master Thesis:	Karlijn Boots	2020
Master Thesis:	Maarten Kolk	2020
Master Thesis:	Sabine Haggenberg	2020
Master Project:	Jisca Sikkenk	2020
Bachelor Thesis:	Julian Jonk	2020
Master Thesis:	Maartje Basten	2021
Master Thesis:	Bridget Slaats	2021
Master Thesis:	Ivar Gast	2021
Master Thesis:	Tijmen Beemster	2021
Master Thesis:	Rania Makkie	2021
Bachelor Thesis:	Najla Boujeddaine	2021

DANKWOORD

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ABOUT THE AUTHOR (CURRICULUM VITAE)

Sebastiaan Blok was born on the first of April 1986 in Eindhoven, where he grew up with his parents Josine and Pim together with his younger brother and sister Thomas and Stella. After graduating from the Van Maerlantlyceum in 2004, he went to Spain to study Spanish for a year.

In 2005 he moved to Amsterdam and started studying the Bèta-Gamma bachelor at the University of Amsterdam, which he combined with Medicine from 2006 onwards. In 2010 he graduated for both bachelors and started the two-year master's program Management, Policy-analysis and Entrepreneurship in Health and Life Sciences at the Vrije Universiteit Amsterdam.

After obtaining his master's degree he started working as consultant at the healthcare sector of KPMG in Amsterdam. In 2015 he joined Cardiologie Centra Nederland (CCN) as operational manager, where he helped setting up the eHealth program HartWacht, which was awarded the *Value Based Healthcare Award* and the *HIMSS – Elsevier Digital Healthcare Award*, both in 2019.

From 2019 to 2021, Sebastiaan combined his role at CCN with a PhD-trajectory, resulting in this thesis. He currently holds the position of Director eHealth at CCN.