International Journal of Epidemiology, 2021, 1–11
doi: 10.1093/ije/dyab210
Original Article

Original Article

How blood pressure predicts frailty transitions in older adults in a population-based cohort study: a multi-state transition model

Daniela Anker ,[1,2]* Cristian Carmeli,[1] Marcel Zwahlen,[3] Nicolas Rodondi,[4,5] Valérie Santschi,[6] Yves Henchoz ,[7] Christina Wolfson[8] and Arnaud Chiolero[1,4,8]

[1]Population Health Laboratory (#PopHealthLab), University of Fribourg, Fribourg, Switzerland, [2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland, [3]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland, [4]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, [5]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [6]La Source, School of Nursing Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Delémont, Switzerland, [7]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland and [8]Department of Epidemiology and Biostatistics and Occupational Health, School of Population and Global Health, McGill University, Montréal, Québec, Canada

*Corresponding author. Population Health Laboratory (#PopHealthLab), University of Fribourg, Route des Arsenaux 41, 1700 Fribourg, Switzerland. E-mail: daniela.anker@unifr.ch

Received 27 January 2021; editorial decision 2 September 2021

Abstract

Background: Low blood pressure (BP) is associated with frailty in older adults. Our aim was to explore how BP predicts transitions between frailty states.
Methods: We used data from the Lausanne cohort Lc65+, a population-based cohort of older adults randomly drawn from a population registry in Switzerland, in 2004, 2009 and 2014. BP was measured using a clinically validated oscillometric automated device and frailty was defined using Fried's phenotype, every 3 years. We used an illness-death discrete multi-state Markov model to estimate hazard ratios of forward and backward transitions between frailty states (outcome) in relation to BP categories (predictor of interest) with adjustment for sex, age and antihypertensive medication (other predictors).
Results: Among 4200 participants aged 65–70 years (58% female) at baseline, 70% were non-frail, 27% pre-frail and 2.0% frail. Over an average follow-up of 5.8 years, 2422 transitions were observed, with 1575 (65%) forward and 847 (35%) backward. Compared with systolic BP (SBP) $<$130 mmHg, the hazard ratio (95% confidence interval) of the transition from non-frail to pre-frail was 0.86 (0.74 to 1.00) for SBP 130–150 mmHg, and 0.89 (0.74 to 1.06) for SBP $\geq$150 mmHg. Compared with SBP $<$130 mmHg, the hazard ratio of the transition from pre-frail to frail was 0.71 (0.50 to 1.01) for SBP 130–150 mmHg, and 0.90 (0.62 to 1.32) for SBP $\geq$150 mmHg. Diastolic BP was a weaker predictor of forward transitions.
Conclusions: BP categories had no strong relationship with either forward transitions or

© The Author(s) 2021. Published by Oxford University Press on behalf of the International Epidemiological Association.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

backward transitions in frailty states. If our findings are confirmed with greater precision and assuming a causal relationship, they would suggest that there is no well-defined optimal BP level to prevent frailty among older adults.

Key words: Blood pressure, frailty, ageing, cohort studies, epidemiology

Key Messages

- Low blood pressure (BP) is associated with frailty in older adults in cross-sectional studies.
- Frailty is a dynamic condition: individuals transition forwards and backwards through several states of progressive severity in frailty.
- An illness-death model allowed us to explore transition rates between three frailty states, i.e. non-frail, pre-frail and frail, and to assess how BP predicts transitions in frailty.
- We found that BP categories had no strong relationship with either forward transitions or backward transitions in frailty states.
- Our findings might suggest that there is no well-defined optimal BP level to prevent frailty among older adults.

Introduction

Several cross-sectional studies have shown that low blood pressure (BP) is associated with frailty in older adults.[1,2] Frailty is a geriatric syndrome of vulnerability and loss of adaptability to stress, predicting an increased risk of adverse health outcomes such as falls, hospitalization and premature death.[3] For instance, in the population-based Lausanne cohort Lc65+ including older adults aged 65 years and more, pre-frail individuals had on average a lower systolic blood pressure (SBP) by 2.7 mmHg and frail individuals by 6.7 mmHg, compared with non-frail individuals.[1]

These findings contribute to the current uncertainties surrounding hypertension management in older adults. Indeed, it is still debated whether intense hypertension management in older adults is beneficial, especially in those who are vulnerable and frail.[4] This translates into discordant recommendations from major international hypertension management guidelines.[5] For instance, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines recommended intensive hypertension management with BP targets below 130/80 mmHg,[6] whereas the 2017 Guidelines by the American College of Physicians and the American Academy of Family Physicians (ACP/AAFP) recommended a more conservative treatment with BP targets below 150/90 mmHg.[7] Investigating how these BP levels predict frailty may help in identifying older adults at risk for the development of frailty according to their BP level. Further, if BP predicts frailty, this could indicate a causal relationship, hence certain BP levels might be detrimental by causing frailty in older adults.

Currently, few studies have investigated the longitudinal relationship between BP and frailty. In these studies, BP did not predict or only weakly predicted incident frailty over time[2]; the dynamic nature of frailty, i.e. the fact that individuals can move back and forth through frailty states, was however not accounted for. In 2019, the *Lancet* published a two-paper series in which the authors called for appropriate statistical methods to capture and account for the dynamics of frailty over time.[3,8] One suitable method to describe the progression of a dynamic condition is multi-state modelling.[9] Multi-state models describe how individuals move through different stages of a disease or a condition.[9] Applied to frailty, multi-state models allow researchers to: (i) incorporate the fact that individuals move between frailty states over time, i.e. non-frail, pre-frail and frail; and (ii) assess how variables such as BP predict transitions between frailty states while accounting for the competing risk of death. Multi-state models may help to better characterize the relationship between BP and the dynamic of frailty.

In this study, our aim was to explore how BP predicts transitions between frailty states over time using a multi-state model applied to data from a cohort study of older adults. We hypothesized that compared with intermediate BP, low BP would predict more forward transitions in frailty states, i.e. worsening health. The current study is, to

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

our knowledge, the first to investigate how BP predicts transitions between frailty states, capturing the dynamic nature of both BP and frailty.

Methods

The Lc65+ study was approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne, Switzerland.

Study population

We used data from the Lausanne cohort Lc65+.[10,11] The cohort was originally designed to investigate frailty and its determinants and evolution over time. Initially, three representative samples of older adults aged 65 to 70 years residing in the city of Lausanne, Switzerland, were invited by mail to participate in 2004, 2009 and 2014 (Supplementary Figure S1, available as Supplementary data at *IJE* online). These samples were drawn at random from the population registry of the city of Lausanne. Individuals living in institutions or not able to respond by themselves to questionnaires due to advanced dementia were excluded. Data were collected through questionnaires every year and through physical and cognitive measurements every 3 years. The physical and cognitive measurements started in 2005 in Lc65+ sample one, 2010 in sample two and 2015 in sample three, and these time points were considered as baseline for the present analyses (Supplementary Figure S2, available as Supplementary data at *IJE* online).

For the statistical analyses, we used data from the three samples up to 2018, i.e. for Lc65+ sample one we used frailty and BP measurements collected in 2005, 2008, 2011, 2014 and 2017; for Lc65+ sample two, we used frailty and BP measurements collected in 2010, 2013 and 2016; and for Lc65+ sample three, we used frailty and BP measurements collected in 2015 and 2018. Data collection was done over the whole year, e.g. in sample three data were collected from 13 February 2015 to 14 December 2015 at baseline, and from 8 February 2018 to 11 December 2018 at 3 years' follow-up. We excluded individuals who died or left the study between recruitment and baseline and those who had fewer than two measurements of frailty over the whole observation period and therefore had no observed transition among the frailty states (Supplementary Figure S1).

Measurement of frailty and blood pressure

Frailty was defined using Fried's phenotype.[12] Fried's phenotype is based on five criteria: weakness, slowness, weight loss, exhaustion and low physical activity. The way these criteria were measured in the Lc65+ study is described in detail elsewhere.[1,10,13] Briefly, weakness and slowness were measured through physical measurements of, respectively, grip strength with a dynamometer and gait speed with a walking test. In some cases when the walking test and the grip strength test could not be performed, slowness and weakness were imputed based on the judgment of the research assistant following pre-established decision algorithms[1]; the decision algorithms are described in Supplementary Boxes S1 and S2, available as Supplementary data at *IJE* online. Weight loss, exhaustion and low physical activity were assessed by self-report. The assessment of frailty was done following a standardized procedure identically applied across follow-ups in the three samples. Three frailty states were defined: (i) non-frail if participants had no criteria fulfilled; (ii) pre-frail if they met one or two criteria; and (iii) frail if they met three or more criteria.

BP was measured at the study centre by trained medical research assistants using a clinically validated oscillometric automated device and following a standardized protocol across years. The detailed procedure is described elsewhere.[1,10,13] Briefly, BP was measured after 10 to 20 min of rest in a sitting position, with a cuff size adapted to the participant's arm circumference, three times at 5–10-min intervals at each follow-up visit. The mean of the three BP measurements was used for our analyses.

We defined BP categories to reflect BP targets in older adults as suggested by two conflicting international hypertension management guidelines: the 2017 ACC/AHA Guideline and the 2017 Guideline by the ACP/AAFP.[10,11] For the primary prevention of cardiovascular disease in community-dwelling older adults, the ACC/AHA 2017 recommended targeting BP below 130/80 mmHg, whereas the ACP/AAFP 2017 recommended targeting below 150/90 mmHg. Hence, we defined three categories of SBP and diastolic BP (DBP): SBP <130 mmHg, $130 \leq$ SBP <150 mmHg, and SBP ≥ 150 mmHg; and DBP <80 mmHg, $80 \leq$ DBP <90 mmHg, and DBP ≥ 90 mmHg, respectively.

Measurement and definition of other variables

Date of birth and sex were taken from the residential registry and date of death was obtained through linkage with death certificates obtained through the canton of Vaud population registry.[10] Antihypertensive medication use was defined for participants, who answered 'yes' to the question: 'Are you currently taking medication at least once a week to lower your blood pressure (hypertension)?'. At baseline, information on self-reported hypertension,

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

other cardiovascular risk factors [hypercholesterolaemia, diabetes, history of cardiovascular disease, smoking status, body mass index (BMI) category], number of chronic conditions, polypharmacy and level of education were collected. Hypertension was defined for participants who reported a diagnosis or use of BP-lowering medication; hypercholesterolaemia as diagnosis or use of cholesterol-lowering medication; diabetes as diagnosis or use of insulin; history of cardiovascular disease as diagnoses of stroke, coronary artery disease or another heart disease or use of medication for the heart; and smoking as current smoking (former- and never-smokers were defined as non-smokers). BMI was defined based on measured weight and height. BMI categories were underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥30.0 kg/m^2). The number of chronic conditions was the sum of the following self-reported conditions: hypertension, hypercholesterolaemia, coronary heart disease, stroke, diabetes, chronic pulmonary disease, osteoporosis, arthrosis, Parkinson's disease and obesity. Participants had polypharmacy if they answered five or more to the question: 'How many different brand name medications do you regularly take at this time?'.[14]

State definition and transitions

We defined four states that included three frailty states, i.e. non-frail, pre-frail and frail, and an absorbing state of death (Figure 1). The state of death is called absorbing because once a participant enters the state, he or she remains in that state. In comparison, the frailty states are not absorbing but transient states, because when a participant is in one of the frailty states, he or she can still move to other states.[9] These states were observed every 3 years and thus were interval censored, i.e. participants were in unknown states between observation times. In Lc65+ sample one, the states were observed at baseline and at 3-, 6-, 9- and 12-year follow-up, that is five observation times with four 3-year intervals in between. In Lc65+ sample two, the states were observed at baseline and at 3- and 6-year follow-up, that is three observation times with two 3-year intervals in between. In Lc65+ sample three, the states were observed at baseline and at 3-year follow-up, that is two observation times with one 3-year interval in between.

An interval was defined by two successive visits with physical measurements, e.g. during the time between baseline and 3-year follow-up. At the beginning of an interval, participants can be in either of the three frailty states. They can stay in the same state, experience a forward or a backward transition to any consecutive frailty state, or die (Figure 1). Transitions were defined when a participant moved from one frailty state to another over time. Transitions could be forwards, i.e. from non-frail to pre-frail or from pre-frail to frail, or backwards, i.e. from frail to pre-frail or from pre-frail to non-frail. Transitions were not observed per se, they occurred during an interval.

Statistical analyses

We computed means and standard deviations (SD) for normally distributed continuous variables, median [minimum to maximum (min–max)] for non-normally distributed continuous variables and counts (percentages) for

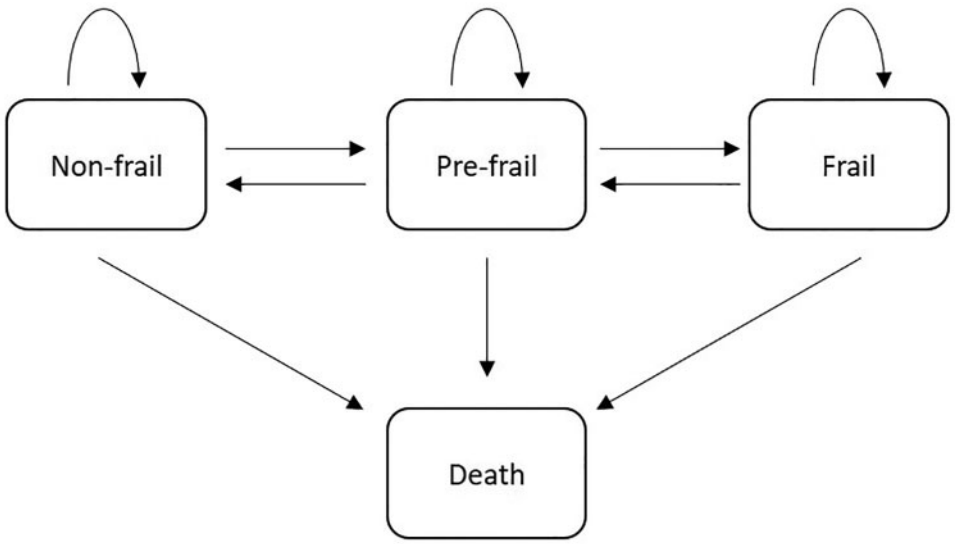

Figure 1 Multi-state transition model; in rectangles are the states, with three frailty states and an absorbing state of death The arrows indicate permitted transitions. Over time, individuals move forward or backward in frailty states, remain in the same frailty state or die

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

categorical variables. We calculated the observed proportions of participants who were alive, dead or dropped out at baseline and at 3-, 6-, 9- and 12-year follow-up. Further, among those alive, we calculated the proportion of non-frail, pre-frail and frail at baseline and at 3-, 6-, 9- and 12-year follow-up. To count the number of consecutive pairs of states, including forward and backward transitions in frailty as well as transitions to death and censored states, we used the state.msm function from the msm package in R. Participants' states were censored if they withdrew from the study, were excluded or lost to follow-up. To visualize transitions between frailty states and death for each of the Lc65+ samples separately, we built flow diagrams (Sankey plot) using the networkD3 package in R. We calculated the total mean person-years (SD; min–max) by adding each participant's time from baseline to death, or censoring.

To model transitions in frailty states over time, we used a discrete multi-state Markov model, applying the msm package in R.[9] The resulting output of the multi-state model is a matrix of instantaneous transition rates between states with hazard ratios for BP categories and other covariates. The underlying Markov assumption is that future transitions in frailty only depend on the current state; the model is memoryless and is not influenced by the history of state transitions prior to the current state. Censored individuals, i.e. excluded or lost to follow-up, were accounted for. One additional assumption is that participants cannot skip a state in the process. It is however possible, e.g. that participants non-frail at the beginning of an interval were directly frail at the end. In these cases, the model implicitly considered that these participants transited through pre-frailty during the interval, even if it had not been recorded.

To investigate the predictive effect of BP (predictor of interest) on transition rates in frailty (outcome), we built several multi-state Markov models[9] with the transition rates regressed on BP category, first unadjusted (model 0) and second adjusted for sex, age category (age <75 years vs age ≥ 75 years) and antihypertensive medication use at baseline (other predictors; model 1). We built separate models for SBP and DBP categories. Age and BP categories were integrated as time-varying covariates, which means that transitions over an interval, e.g. from baseline to 3-year follow-up, were regressed on the age and BP categories measured at baseline, with both assumed to stay constant over the interval.[9]

We verified the assumption of constant transition rates through visual checking, comparing observed against predicted proportions of frailty states and death over time.[5] Where the assumption held, i.e. the proportions of observed and predicted states remained similar over time, we would keep the time-homogeneous model, i.e. with constant transition rates over the observation period. Where the assumption did not hold i.e. there were large discrepancies between the proportion of observed and predicted states over time, we would create a time-non-homogeneous model, i.e. with piecewise constant transition rates over the observation period (model 2).

To assess potential selection bias, we compared baseline characteristics of participants in the analytical sample with participants excluded because they had fewer than two measurements of frailty over the observation period (Supplementary Table S1, available as Supplementary data at *IJE* online). To address missing data, we computed the proportion of missing data in frailty assessments at each data collection time point and summarized them in Supplementary Table S2, available as Supplementary data at *IJE* online. For baseline characteristics, missing data in self-reported hypertension diagnosis, antihypertensive medication intake, variables defining other cardiovascular risk factors, variables defining the number of chronic conditions and the variable defining polypharmacy were interpreted as absence of those characteristics. For the analyses, other missing data were left as they were. In the multi-state transition models, missing observations were censored.[9]

Results

Out of 15 175 residents of the city of Lausanne, Switzerland, aged 65 to 70 years, 9887 were invited to participate in the Lc65+ cohort study and 4731 (48% of invited) agreed to participate. In all 459 (10%) individuals were excluded from the analytical sample as they died or were lost to follow-up, and 72 (1.5%) individuals were excluded because they had fewer than two measurements of frailty over the observation period. Some 4200 participants (58% females) were included in the present analyses (Supplementary Figure S1). At baseline, the median (min–max) age was 69 (66–71) years. The mean BP [SBD (SD)/DBP(SD)] was 137(19)/79(11) mmHg and 37% of participants reported taking antihypertensive medication (Table 1). At baseline, the proportions of non-frail, pre-frail and frail were 70%, 27% and 2.0%, respectively. At 3-, 6-, 9- and 12-year follow-up, the proportions of individuals with frailty were 2.8%, 3.7%, 4.4% and 8.4%, respectively (Supplementary Table S2). The proportion of individuals for whom frailty was assessed using the pre-established imputation algorithm was below 5% at baseline and reached about 10% among the participants who were followed-up for the longest period of time, i.e. 12 years (data not shown). The participants who were excluded because they had fewer than two measurements of frailty were slightly less educated and were overall slightly less healthy than individuals in the analytical sample (Supplementary Table S1).

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

Table 1 Baseline characteristics of participants

Characteristics		*N* (%)
Total *N*		4200 (100%)
Sex	Women	2442 (58%)
	Men	1758 (42%)
Age (years), median (min–max)		69 (66–71)
Frailty status	Non-frail	2956 (70%)
	Pre-frail	1153 (27%)
	Frail	84 (2.0%)
	Missing	7 (0.2%)
Sysolic BP [mmHg], mean (SD)		137 (19)
Sysolic BP category	SBP <130	1378 (33%)
	130 ≤ SBP <150	1531 (36%)
	SBP ≥150	926 (22%)
Diastolic BP [mmHg], mean (SD)		79 (11)
Diastolic BP category	DBP <80	2055 (49%)
	80 ≤ DBP <90	1140 (27%)
	DBP ≥90	640 (15%)
	Missing in BP	365 (8.7%)
Hypertension		1755 (42%)
Hypertension treatment		1568 (37%)
Other cardiovascular risk factors		
Hypercholesterolaemia		1592 (38%)
Diabetes		409 (9.7%)
History of cardiovascular disease		779 (19%)
Smoking status		769 (18%)
BMI category	Underweight	56 (1.3%)
	Normal weight	1335 (32%)
	Overweight	1556 (37%)
	Obese	883 (21%)
	Missing	370 (8.8%)
Number of chronic diseases	0	899 (21%)
	1	1242 (30%)
	≥2	2059 (49%)
Polypharmacy		688 (16%)
Education	Basic compulsory	811 (19%)
	Apprenticeship	1642 (39%)
	High school	1008 (24%)
	University	730 (17%)
	Missing	9 (0.2%)

Values are numbers (%) unless indicated otherwise. *N*, number of participants; SD, standard deviation; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; polypharmacy, five categories of medications at least once a week.

Over 24 483 person-years of follow-up, with a mean (SD; min–max) follow-up per participant of 5.8 (5.2; 3–12) years, we observed 2422 transitions. Of those, 1575 (65%) were forward transitions—1336 (55%) transitions from non-frail to pre-frail and 179 (7.4%) from pre-frail to frail states—and 847 (35%) were backward transitions—82 (3.4%) transitions from frail to pre-frail and 755 (31%) from pre-frail to non-frail states (Table 2). Supplementary Table S3, available as Supplementary data at *IJE* online, shows all observed pairs of consecutive states (frailty states, death), including those who moved to a censored state. Among non-frail, pre-frail and frail individuals, 118, 172 and 36 transitions to death were observed, respectively. These transitions represented 2.1%, 6.7% and 17% of all transitions among those who were, respectively, non-frail, pre-frail and frail at the beginning of the interval. Among non-frail, pre-frail and frail individuals, 284, 160 and 20 participants, respectively, moved to a censored state. These transitions represent 5.1%, 6.3% and 9.3% of all transitions among those who were, respectively, non-frail, pre-frail and frail at the beginning of the interval. Figure 2 shows a flow diagram of state transitions in sample one of the Lc65+ cohort and Supplementary Figure S3, available as Supplementary data at *IJE* online shows flow diagrams in samples two and three.

Table 2 Number (%) of observed forward transitions and backward transitions in frailty states over 24 483 person-years of follow-up, i.e. a mean (SD) follow-up per participant of 5.8 (5.2) years

Transitions	*N* (%)
Forward	1575 (65%)
Non-frail to pre-frail	1336 (55%)
Non-frail to frail	60 (2.5%)
Pre-frail to frail	179 (7.4%)
Backward	847 (35%)
Pre-frail to non-frail	755 (31%)
Frail to pre-frail	82 (3.4%)
Frail to non-frail	10 (0.4%)
Forward and backward	2422 (100%)

Percentage was computed in relation to the total number of forward and backward transitions, respectively.
N = number of transitions.

Through visual checking,[9] we compared observed and predicted proportions of frailty states and death over time for the adjusted time-homogeneous multi-state model (model 1) and concluded that the assumption of constant transitions rates did not hold (Supplementary Figure S4, available as Supplementary data at *IJE* online). This model's predictions overestimated the proportion of frailty states at the expense of underestimating the proportion of death at 12-year follow-up. Hence, we based our final estimates on a time-non-homogeneous model with piecewise constant transition rates for the periods from baseline to 9 years, and from 9 to 12 years (model 3). Table 3 summarizes hazard ratios of forward transitions in frailty states by SBP (panel A) and DBP (panel B) for model 0, model 1 and model 2.

In the time-non-homogeneous model, adjusted for sex, age category and antihypertensive medication use (model 2), compared with SBP <130 mmHg, the hazard ratio

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

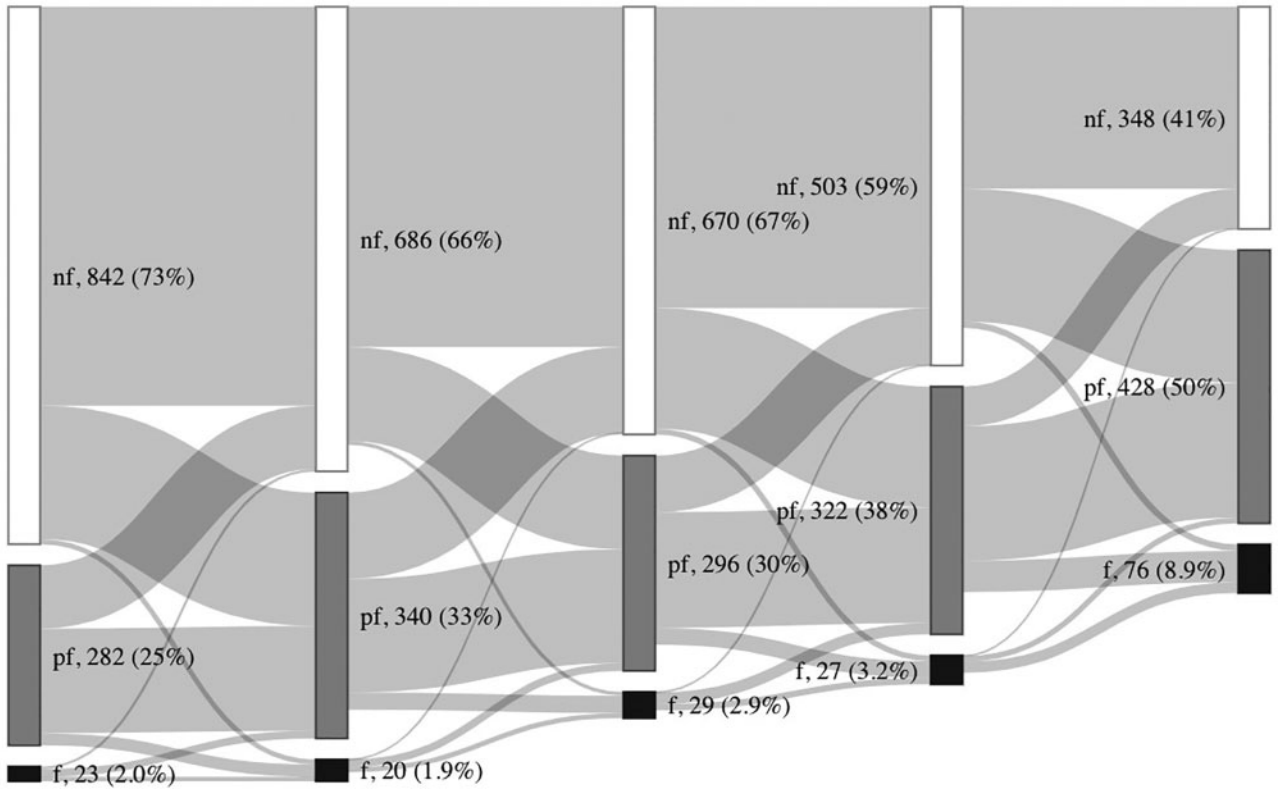

Figure 2 Transitions in frailty states in sample one of the Lc65+ cohort. Baseline 3 years (yrs) of follow-up (f-u), 6 yrs f-u, 9 yrs f-u, 12 yrs f-u. Numbers are participant counts in each frailty state (%), i.e. non-frail (nf), pre-frail (pf) and frail (f)

[95% confidence interval (CI)] of the transition from non-frail to pre-frail was 0.86 (0.74 to 1.00) for SBP 130–150 mmHg and 0.89 (0.74 to 1.06) for SBP ≥ 150 mmHg. Compared with SBP <130 mmHg, the hazard ratio of the transition from pre-frail to frail was 0.71 (0.50 to 1.01) for SBP 130–150 mmHg and 0.90 (0.62 to 1.32) for SBP ≥150 mmHg.

Further, compared with DBP <80 mmHg, the hazard ratio of the transition from non-frail to pre-frail was 0.90 (0.77 to 1.04) for DBP 80–90 mmHg and 0.93 (0.76 to 1.13) for DBP ≥90 mmHg. Compared with DBP <80 mmHg, the hazard ratio of the transition from pre-frail to frail was 1.01 (0.70 to 1.44) for DBP 80–90 mmHg and 1.03 (0.65 to 1.63) for DBP ≥90 mmHg (Table 3). Hazard ratios of backward transitions (frail to pre-frail and pre-frail to non-frail) by BP categories can be found in Supplementary Table S4, available as Supplementary data at *IJE* online.

Discussion

Our study showed that among transitions in frailty states, about two-thirds were forward and one-third was backward. We found that BP categories had no strong relationship with either forward transitions or backward transitions in frailty states. Our findings are, however, subject to uncertainty as revealed by the wide confidence intervals around point estimates.

Several studies, cross-sectional or longitudinal, have been conducted on the relationship between BP and frailty. Longitudinal studies investigated how BP predicts frailty over time using time-to-event analysis, which only captures forward transitions or analyses of association using odds ratios or risk ratios.[2] In a study by Bouillon *et al.*, hypertension (BP ≥130/85 mmHg or antihypertensive medication use) predicted an increased probability of being frail or pre-frail at 10 years [unadjusted odds ratio (OR), 95% CI: 1.25, 1.06 to 1.46].[15] In a time-to-event analysis by Barzilay *et al.*, increased BP (≥130/85 mmHg) at baseline predicted the incidence of frailty in univariate analyses [hazard ratio (HR), 95% CI: 1.16, 1.01 to 1.33].[16] Therein the associations became weaker when adjusted for other cardio-metabolic and health-related variables. These studies were, however, not designed to specifically characterize how BP predicts frailty. The study by Bouillon *et al.* failed to disentangle the effect of antihypertensive medication

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

Table 3 Hazard ratios (95% confidence interval) of forward transitions in frailty states by systolic blood pressure (SBP) and diastolic blood pressure (DBP) category. Panel A are transitions by SBP category and panel B by DBP category

A						
Model	State transition	SBP <130	130 ≥ SBP <150	SBP ≥150	Women	Antihypertensive medication
Model 0	Non-frail to pre-frail	1	0.91 (0.78 to 1.05)	0.96 (0.81 to 1.14)	–	
	Pre-frail to frail	1	0.65 (0.45 to 0.95)	1.06 (0.67 to 1.65)	–	
Model 1	Non-frail to pre-frail	1	0.90 (0.78 to 1.03)	0.96 (0.81 to 1.14)	1.10 (0.97 to 1.24)	
	Pre-frail to frail	1	0.66 (0.46 to 0.95)	1.00 (0.67 to 1.48)	1.12 (0.79 to 1.58)	
Model 2	Non-frail to pre-frail	1	0.86 (0.74 to 1.00)	0.89 (0.74 to 1.06)	1.17 (1.03 to 1.33)	1.30 (1.14 to 1.48)
	Pre-frail to frail	1	0.71 (0.50 to 1.01)	0.90 (0.62 to 1.32)	1.18 (0.85 to 1.64)	1.63 (1.21 to 2.21)
B						
Model	State transition	DBP <80	80 ≥ DBP <90	DBP ≥90	Women	Antihypertensive medication
Model 0	Non-frail to pre-frail	1	0.87 (0.75 to 1.00)	0.92 (0.70 to 1.19)	–	
	Pre-frail to frail	1	0.91 (0.61 to 1.37)	1.13 (0.64 to 2.01)	–	
Model 1	Non-frail to pre-frail	1	0.90 (0.78 to 1.04)	0.96 (0.79 to 1.15)	1.11 (0.98 to 1.25)	
	Pre-frail to frail	1	1.09 (0.76 to 1.56)	1.17 (0.73 to 1.89)	1.22 (0.87 to 1.71)	
Model 2	Non-frail to pre-frail	1	0.90 (0.77 to 1.04)	0.93 (0.76 to 1.13)	1.18 (1.04 to 1.35)	1.28 (1.12 to 1.46)
	Pre-frail to frail	1	1.01 (0.70 to 1.44)	1.03 (0.65 to 1.63)	1.22 (0.87 to 1.70)	1.62 (1.20 to 2.18)

Blood pressure category was accounted for as a time-varying covariate and blood pressure values are in mmHg. Model 0: unadjusted; model 1: adjusted for sex and age category (age <75 years; age ≥75 years); model 2: time-non-homogeneous with piecewise constant transitions from baseline to 9 years and from 9 to 12 years, adjusted for sex, age category (age <75 years; age ≥75 years) and antihypertensive medication use at baseline.

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

and BP. Further, since frailty is a dynamic condition with frequent forward and backward transitions, a time-to-event approach may not be appropriate.

The current study is, to our knowledge, the first to investigate how BP predicts—prospectively—transitions between frailty states, capturing the dynamic nature of both BP and frailty. The main strength of our study is the use of multi-state modelling to assess the predictive value of BP on transitions in frailty, based on observed states. BP was integrated as a time-varying covariate, which allowed accounting for changes in BP over time notably for a potential end-of-life BP decline,[17,18] and transition rates were modelled in a piecewise constant manner, taking into account strong increase in death rates with advancing age.

Additional strengths of our study are its population-based sampling, the long follow-up, and the accuracy of the data.[10] Specifically, the components of frailty and BP were collected over time following a standardized protocol kept identical across years. Furthermore, data collection in the Lc65+ was done at fixed intervals specified in advance. That kind of observation scheme, compared with patient self-selection, avoids bias in the estimation of transition rates because data were collected independently of disease progression.[9,19] In contrast, in observational schemes relying on patient self-selection, e.g. data collected at the hospital during routine clinical practice, individuals experiencing disease progression may be over-represented compared with those who stay healthy over time, thus leading to an overestimation of forward transition rates.[19]

One limitation of our study is the Markov assumption underlying the multi-state models. The Markov assumption implies that future transitions in frailty only depend on the current state.[9] This may not necessarily be the case, but as we plotted the observed against the estimated proportion of states, we saw that the model fits the data reasonably well (Supplementary Figure S4, available as Supplementary data at *IJE* online). Further, although our method requires that some participants transit from non-frail to frail or the opposite in a single transition, our model assumes that individuals can only transit between consecutive states. This may be wrong, but since frailty is considered a progressive syndrome of continuously

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

depleting energy that develops with older age,[12] this assumption seems credible in the majority of the cases. Another limitation is that frailty and BP were measured only every 3 years and not on a continuous basis. Hence, transitions were not observed per se; instead, they were assessed based on observed states at the times of study visits.

Another potential limitation in our study is related to the known possibility of convergence failure in complex models. To mitigate this possibility, we included a small number of covariates in the multi-state transition models, and we categorized both age and BP rather than including them as continuous covariates. Adjusting for potential predictors of frailty (e.g. income, unhealthy lifestyle, multimorbidity[20]) or potential confounders of the relationship between BP and frailty (e.g. cardiovascular risk factors) would have allowed us to better isolate the predictive effect of BP on frailty devoid of the effect of other predictors and accounting for some confounding. Furthermore, including BP and age as continuous covariates, e.g. using splines to model non-linear effects, could have resulted in a more precise predictive model of BP on frailty. Multi-state transition models are, however, limited in the number and complexity of variables that can be included simultaneously, as complex models often fail to reach convergence.[9] A further limitation is the use of self-reported data for several baseline characteristics, notably chronic conditions. The information about chronic conditions might have been more accurate if collected from medical health records.[21]

Other limitations of our study are the relatively low proportion of frailty and the potential impact of selection bias. The proportion of frailty was 2.0% among participants aged 67 to 71 years and 8.4% among participants aged 78–83 years. In a systematic review including studies on community-dwelling older adults aged 65 years and more in high-income countries and using Fried's phenotype to operationalize frailty, the pooled prevalence estimates ranged between 4% and 17%.[22] Across age categories, the estimates were 4.1% (95% CI: 3.4 to 4.8) in the 65–69 age group, 6.8% (95% CI: 5.7 to 7.9) in the 70–74, 9.9% (95% CI: 8.6 to 11.2) in the 75–79, 15.7% (95% CI: 13.5 to 17.9) in the 80–84 and 26.1% (95% CI: 22.1 to 30.1) in the 85 years and more group.[22] These estimates are higher than ours. This difference might be due to some selection bias. First, 52% of individuals invited to the study refused to participate. Second, 72 individuals were excluded from the analytical sample (1.5% of the cohort) because they had fewer than two assessments of frailty throughout the follow-up. Third, attrition increased over time and reached 14% at 12-year follow-up. Fourth, missing data were not imputed in this analysis. Hence, taken together, our findings are subject to selection bias through healthy participant, attrition and healthy survivor biases. Nevertheless, the age and sex distributions of the Lc65+ cohort samples were not different from the sampled population.[23,24] It is also possible that the prevalence of frailty is relatively low in Switzerland; using data from the Survey of Health, Aging and Retirement in Europe (SHARE), Santos-Eggimann *et al.* reported a lower prevalence of frailty in Switzerland compared with other European countries.[25]

Our findings raise the question as to what is the optimal BP level in older adults. We found that BP categories had no strong relationship with either forward transitions or backward transitions in frailty states. Our findings are, however, subject to large uncertainty as revealed by the wide confidence intervals around point estimates. This suggests that we have a relatively small sample to address our research question. A larger sample would be needed to confirm or refute our findings, e.g. the Canadian Longitudinal Study on Aging (CLSA) that follows up 50 000 individuals aged between 45 and 85 years.[26] Another data source may be electronic health records and administrative claims data, although identifying frailty in such data remains challenging.[27] Increasing the sample size would eventually allow the construction of more complex models, including BP as a continuous variable instead of a categorical one, with adjustment for several confounding factors without convergence failure.

If our findings were to be confirmed with greater precision and assuming a causal relationship between BP and frailty, they would suggest that there is no optimal BP to prevent frailty among older adults.[28] Further studies are needed to investigate the causal relationship between BP and frailty. These studies may eventually give some further indication on how to account for frailty in the management of hypertension in older adults.

To conclude, the current study is, to our knowledge, the first to investigate how BP predicts transitions between frailty states, capturing the dynamic nature of both BP and frailty. The multi-state illness-death model allowed us to investigate the relationship between BP and frailty in a dynamic system with multiple states, encompassing both forward and backward transitions. We found that BP categories did not strongly predict transitions in frailty states. Due to the large uncertainty in our findings, further studies are needed to confirm or not the absence of optimal BP for the prevention of frailty.

The data can be acquired through the Lc65+ study investigators. The computing codes are available upon request to the corresponding author.

Supplementary Data

Supplementary data are available at *IJE* online.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

Funding

D.A. was partly funded by the Swiss National Science Foundation for this work (grant number P1BEP3_188171). The Lc65+ study was supported by: University of Lausanne Hospital Centre; University of Lausanne Department of Ambulatory Care and Community Medicine; Canton de Vaud Department of Public Health; City of Lausanne; Loterie Romande (research grants 2006–08 and 2018–19); Lausanne University Faculty of Biology and Medicine [multidisciplinary research grant 2006]; Swiss National Foundation for Scientific Research [grant 3247B0-120795/1]; Fondation Médecine Sociale et Préventive, Lausanne; and the Leenaards Foundation. The sponsors had no role in the design, execution, analysis and interpretation of data or writing of the study.

Acknowledgements

The authors would like to thank Prof. Brigitte Santos-Eggimann for granting access to the data from the Lausanne cohort Lc65+ cohort and for her intellectual input and constructive comments on the research project.

Author Contributions

All authors contributed to the study concept and design. Data preparation and analysis were performed by D.A., A.C. and C.C. The first draft of the manuscript was written by D.A. and A.C. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

References

1. Anker D, Santos-Eggimann B, Zwahlen M *et al.* Blood pressure in relation to frailty in older adults: a population-based study. *J Clin Hypertens* 2019;**21**:1895–904.
2. Vetrano DL, Palmer KM, Galluzzo L *et al.*; Joint Action ADVANTAGE WP4 group. Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open* 2018;**8**:e024406.
3. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet* 2019;**394**:1365–75.
4. Benetos A, Bulpitt CJ, Petrovic M *et al.* An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of hypertension in very old, frail subjects. *Hypertension* 2016;**67**:820–25.
5. Anker D, Santos-Eggimann B, Santschi V *et al.* Screening and treatment of hypertension in older adults: less is more? *Public Health Rev* 2018;**39**:26.
6. Whelton PK, Carey RM, Aronow WS *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018;**138**:e484–e594.
7. Qaseem A, Wilt TJ, Rich R *et al.*; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2017;**166**:430–37.
8. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *Lancet* 2019;**394**:1376–86.
9. Jackson C. Multi-state models for panel data: The msm Package for R. *J Stat Softw* 2011;**38**:28.
10. Santos-Eggimann B, Karmaniola A, Seematter-Bagnoud L *et al.* The Lausanne cohort Lc65+: a population-based prospective study of the manifestations, determinants and outcomes of frailty. *BMC Geriatr* 2008;**8**:20.
11. Unisanté. *The Lc65+ Cohort*. https://www.lc65plus.ch/en (10 September 2021, date last accessed).
12. Fried LP, Tangen CM, Walston J *et al.*; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–56.
13. Anker D, Santos-Eggimann B, Zwahlen M *et al.* Blood pressure control and complex health conditions in older adults: impact of recent hypertension management guidelines. *J Hum Hypertens* 2021;**35**:280–89.
14. Benetos A, Rossignol P, Cherubini A *et al.* Polypharmacy in the aging patient: management of hypertension in octogenarians. *JAMA* 2015;**314**:170–80.
15. Bouillon K, Kivimäki M, Hamer M *et al.* Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. *J Am Med Dir Assoc* 2013;**14**:851.e1-6–851.e6.
16. Barzilay JI, Blaum C, Moore T *et al.* Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med* 2007;**167**:635–41.
17. Delgado J, Bowman K, Ble A *et al.* Blood pressure trajectories in the 20 years before death. *JAMA Intern Med* 2018;**178**:93–99.
18. Ravindrarajah R, Hazra NC, Hamada S *et al.* Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. *Circulation* 2017;**135**:2357–68.
19. Grüger J, Kay R, Schumacher M. The validity of inferences based on incomplete observations in disease state models. *Biometrics* 1991;**47**:595–605.
20. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Determinants of frailty. *J Am Med Dir Assoc* 2010;**11**:356–64.
21. Hale MD, Santorelli G, Brundle C, Clegg A. A cross-sectional study assessing agreement between self-reported and general practice-recorded health conditions among community dwelling older adults. *Age Ageing* 2019;**49**:135–40.
22. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012;**60**:1487–92.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021

23. Unisanté. *The Lc65+ Cohort. Representativeness*. https://www.lc65plus.ch/en/content/representativeness (10 September 2021, date last accessed).
24. Abolhassani N, Santos-Eggimann B, Büla C, Goy R, Guessous I, Henchoz Y. Quality of life profile in three cohorts of community-dwelling Swiss older people. *BMC Geriatr* 2019;**19**:96.
25. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci* 2009;**64**:675–81.
26. Raina P, Wolfson C, Kirkland S *et al*. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). *Int J Epidemiol* 2019;**48**:1752–53j.
27. Nghiem S, Sajeewani D, Henderson K *et al*. Development of frailty measurement tools using administrative health data: a systematic review. *Arch Gerontol Geriatr* 2020;**89**:104102.
28. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension* 2014;**63**:433–41.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab210/6398053 by guest on 28 December 2021