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Blood pressure in relation to frailty in older adults: A population-based study

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Abstract

In frail older adults, low blood pressure (BP) might be associated with worse health outcomes and hypertension management in this population is highly debated. Using data from a population-based study of older adults, we assessed the association between frailty and BP. We used data collected between 2014 and 2016 from 3157 participants aged between 67 and 80 years in the Lausanne cohort Lc65+. BP was measured three times at one visit, and frailty status was assessed based on Fried's phenotype model. We analyzed the cross-sectional association between BP and frailty by computing mean systolic and diastolic BP stratified by sex, age, and frailty and by fitting regression models. The average age of the participants was 73.3 (standard deviation [SD]: 4.1) years, and 59.1% were women. 34.1% were pre-frail, and 3.3% were frail. Mean BP was 135.1/76.3 mm Hg (SD 18.5/11.0). Age- and sex-adjusted systolic BP was on average lower by 2.8 mm Hg (95% confidence interval [CI]: 1.4-4.2) and 6.7 mm Hg (95% CI: 3.2-10.3) among pre-frail and frail compared to non-frail participants. Similar differences in mean diastolic BP across frailty status were found. Upon adjustment for antihypertensive treatment, the associations between frailty status and BP did not change substantially. Frail individuals had a substantially lower BP compared with non-frail older adults. Because low BP could be detrimental among frail older patients, our findings raise questions about hypertension management in this population and stress the need for additional evidence.

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1 | INTRODUCTION

Lowering blood pressure (BP) is known to be beneficial in middle-aged adults, but recent research suggests that the benefit is questionable in older adults depending on their health status.[1,2] Numerous trials have shown that lowering BP decreases the risk of cardiovascular disease (CVD) and mortality in middle-aged adults.[3-6] In older adults, however, the evidence is scarce. While two trials including participants aged 75 or 80 years and over have shown that lowering BP reduced all-cause mortality and cardiovascular mortality,[7,8] several cohort studies have shown that older individuals with relatively low BP had higher mortality rates and worse physical and cognitive abilities compared to older individuals with higher BP.[9-11] Hence, how to manage high BP among older adults remains highly debated, including in recent major guidelines.[4,5]

In older adults, frailty may modify the relationship between BP and health outcomes.[1,12,13] Frailty is a multidimensional geriatric syndrome characterized by increased vulnerability and loss of adaptability to stress.[14-16] It is associated with an increased risk of falls, delirium, disability, and mortality.[15,17] In a cohort study, van Hateren et al showed that frail participants with high BP had lower mortality rates compared to frail participants with low BP.[13] In another cohort study, Odden et al showed that fast walking participants—considered as non-frail—with high BP had higher cardiovascular mortality rates compared to those with low BP; among slow walking participants—considered as frail—there was no difference in cardiovascular mortality rates across levels of BP.[12] This suggests that a relatively low BP might be not beneficial and may even be detrimental in frail older adults.

At the population level, the relationship between frailty, BP, and antihypertensive treatment remains poorly described.[1] Using data from a population-based study,[16] we assessed the cross-sectional association between BP and frailty in individuals aged between 67 and 80 years.

2 | METHODS

2.1 | Population

We analyzed data from participants in the Lausanne cohort Lc65+, a population-based study of community-dwelling older adults. The Lc65+ was designed primarily to investigate the determinants, evolution, and outcomes of frailty.[16] A total of 4731 randomly selected community-dwelling residents of the city of Lausanne, Switzerland, were recruited at age 65-70 years in three waves at three different time points: sample 1 (C1) in 2004, sample 2 (C2) in 2009, and sample 3 (C3) in 2014.[18] Follow-up is ongoing. Individuals were excluded if they were living in an institution or if they were unable to respond by themselves to questionnaires due to advanced dementia.

2.2 | Data collection

Data were collected by means of self-administered mailed questionnaires, in-person interviews, and anthropometric measurements. Performance tests were conducted by trained research assistants at the study center, and, in some cases, at participants' homes. For this analysis, we used data collected at baseline and at the most recent data collection for the three samples. The most recent data collection for the samples C1, C2, and C3 took place in 2014, 2016, and 2015, respectively. Details of time points of data collection for each variable included in the analyses are given in Table S1 in the Supporting Information.

2.3 | Blood pressure measurement and definition of hypertension

Blood pressure was measured following a standardized protocol kept identical across years in the three samples. Measures were made at the study center by trained medical research assistants using a clinically validated oscillometric automated device (Omron® 907 (HEM-907-E) digital automatic blood pressure monitor).[19,20] In case of heart rhythm abnormalities, BP was measured using the auscultatory method with an Erkameter 3000® mercury tensiometer and a Duophon® or a Littmann® stethoscope. After 10-20 minutes of rest in a sitting position, BP was measured three times at 5-10 minutes intervals with a cuff size adapted to the participant's arm circumference. Three cuff sizes were available: 17-22 cm (HEM-CS19) for arm circumference less than 22 cm, 22-32 cm (HEM-CR19) for arm circumference between 22 and 32 cm, and 32-42 cm (HEM-CL19) for arm circumference 33 cm and larger. BP was measured on the left arm. During the measurement, the participant was relaxed, sitting comfortably with his or her back supported, left arm resting on a support at level of the heart, and with the palm of the hand up.[16]

Participants were classified as hypertensive (self-reported) if they answered "yes" to following questions: "Has a doctor ever told you that you have too high a blood pressure (hypertension)" or "Are you currently taking any medication to lower your blood pressure (hypertension) at least once a week?". We have also explored further definitions of hypertension, respectively, elevated BP by computing the number of participants with BP ≥ 140/90 mm Hg and the number of participants with BP ≥ 140/90 mm Hg OR self-reported antihypertensive use.

2.4 | Frailty definition and measurement

Frailty was assessed according to Fried's phenotype model following a standardized procedure kept identical across years in the three samples.[16,21] Fried's phenotype model is based on five characteristics, that is, shrinking, exhaustion, weakness, slowness, and low activity. Shrinking was identified if the participant reported any unintentional weight loss in the prior year. Exhaustion was identified if a participant answered "a lot," as compared to "not at all" or "a little," to the question "did you have feelings of generalized weakness, weariness, lack of energy in the last four weeks?". Weakness was identified if the highest value of three measures of grip strength was considered as low. Low grip strength was identified when participants' measures were below certain sex- and body

mass index-specific cut-off values, as defined in the Cardiovascular Health study.[21] Grip strength was measured on the right hand with a DHD-3 Digital Hand Dynamometer SAEHAN® Baseline® hydraulic dynamometer.[22] Walking speed was measured at the study center and slowness was identified if the participant had a low walking speed over 20 meters. Low walking speed was identified when participants' measures were below certain sex- and height-specific cut-off values, as defined in the Cardiovascular Health study.[21] In some cases, slowness was imputed based on the judgment of the research assistant following a decision algorithm. Briefly, the decision algorithm included three criteria: The use of walking aids, the opinion of a medical assistant on whether the participant's gait speed was slowed down, difficult or impossible, and the participant's performance in getting up from a chair. Low activity was identified if the participant reported less than 20 minutes of sport activity once a week and less than 30 cumulated minutes of walking per day three times a week and avoiding to climb stairs or carrying light loads in daily activities. Participants were classified as non-frail, pre-frail, or frail if they had none, one to two, or three to five of these characteristics, respectively.[16]

2.5 | Assessment of other characteristics

Hypercholesterolemia was defined if participants reported taking cholesterol-lowering medication or having been diagnosed with high cholesterol by a physician. Diabetes was defined if participants reported taking medication for diabetes or having been diagnosed with diabetes by a physician. History of CVD was defined if participants reported having been diagnosed with coronary heart disease, stroke, heart insufficiency, cardiomyopathy, heart valve disease, or other cardiopathy, or if they reported taking medication for the heart. Participants were interviewed about the presence of the following chronic diseases: arthrosis, Alzheimer's disease, asthma, cancer, heart failure, coronary heart disease, chronic pulmonary disease, Parkinson's disease, ulcer, HIV, osteoporosis, hypertension, hypercholesterolemia, and diabetes. Functional status was assessed using Katz' basic activities of daily living (BADL) and Lawton's instrumental activities of daily living (IADL).[23,24] To assess BADL, participants were asked if they had "no difficulties," "difficulties but not receiving help," or "difficulties and receiving help" with following activities: taking a bath or a shower, eating, getting in and out of bed or sofa, dressing, and using the toilet. To assess IADL, participants were asked if they had "no difficulties," "difficulties but not receiving help," or "difficulties and receiving help" with following activities: doing light housework, cooking, making phone calls, taking medication, shopping, and taking care of finances. Polypharmacy was defined if participants reported taking five types of medications at least once a week.[2] Financial difficulties were defined if participants reported having had financial difficulties in the past 12 months, having trouble making ends meet, receiving means-tested subsidies for health insurance or receiving complementary financial support in addition to old-age pension.

2.6 | Statistical analyses

We used data from all the participants of the Lc65+ who were still enrolled in the study and who participated at the most recent data collection. To assess the cross-sectional association between BP and frailty, we restricted the analytical sample to the set of participants with complete data for all variables that we selected for our final regression models. First, we computed the number of participants (%) with hypertension and antihypertensive treatment use, stratified by sex, age and frailty. Second, we analyzed the association between BP and frailty by computing mean (SD) systolic BP and mean (SD) diastolic BP stratified by sex, age and frailty. Third, we analyzed the association between BP and frailty by fitting multivariable linear regression models. For systolic BP and diastolic BP, separately, we fitted similar sets of three hierarchical linear regression models. In model 1, BP was regressed on frailty status (dummy variable), adjusted for age and sex. In model 2, estimates were additionally adjusted for socio-economic characteristics (education, Swiss citizenship, financial difficulties, living alone), CVD risk factors (hypercholesterolemia, diabetes, history of CVD, smoking), and body mass index (BMI). In model 3, estimates were additionally adjusted for antihypertensive medication use. We used Stata 14® (Stata Corp) for all analyses.

3 | RESULTS

Figure 1 is a flowchart with the number of participants recruited in each sample (C1, C2, and C3), the number and reasons for dropouts between recruitment and most recent data collection, and the number of participants not considered in the analyses due to missing data. Briefly, out of the 4731 individuals initially recruited in 2004, 2009, and 2014, 3651 individuals participated in the most recent data collection and 3157 had complete data and were included in our analyses (see Table S2 in the Supporting Information for detailed flowcharts separately for each of the three samples). There was no major difference in main baseline characteristics between participants with and without missing data (see Table S3 in the Supporting Information). In the analytical sample, slowness was imputed for 60 participants (1.9%). The main reason was a follow-up done outside of the study center, where a walking test could not be performed.

Table 1 summarizes baseline characteristics of the participants. Some 2157 were women (59.1%), and 1494 were men (40.9%). Mean age of participants was 73.3 (SD: 4.1) years. Some 2226 (61.0%) were non-frail, 1243 (34.1%) pre-frail, and 121 (3.3%) frail. Mean BP was 135.1/76.3 mm Hg (SD 18.5/11.0). Some 1867 (51.1%) reported diagnosed hypertension, and 1601 (43.9%) reported that they were using antihypertensive medication.

Table 2 shows that the proportion of participants with hypertension tended to be higher in men compared to women and increased with age. The proportion of hypertension and use of antihypertensive treatment increased across categories of frailty status.

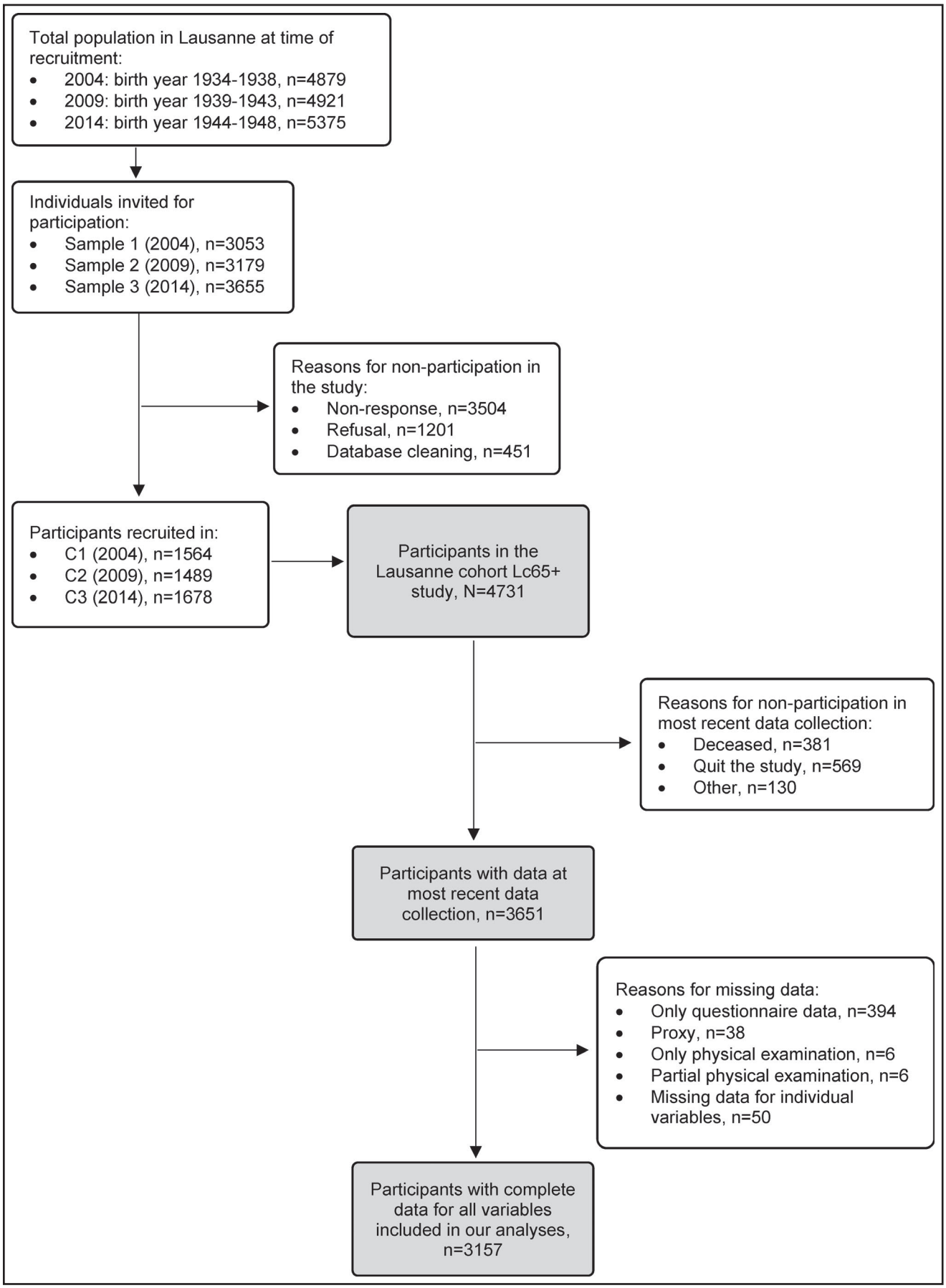
Total population in Lausanne at time of recruitment:
2004: birth year 1934-1938, n=4879
2009: birth year 1939-1943, n=4921
2014: birth year 1944-1948, n=5375
Individuals invited for participation:
Sample 1 (2004), n=3053
Sample 2 (2009), n=3179
Sample 3 (2014), n=3655
Reasons for non-participation in the study:
Non-response, n=3504
Refusal, n=1201
Database cleaning, n=451
Participants recruited in:
C1 (2004), n=1564
C2 (2009), n=1489
C3 (2014), n=1678
Participants in the Lausanne cohort Lc65+ study, N=4731
Reasons for non-participation in most recent data collection:
Deceased, n=381
Quit the study, n=569
Other, n=130
Participants with data at most recent data collection, n=3651
Reasons for missing data:
Only questionnaire data, n=394
Proxy, n=38
Only physical examination, n=6
Partial physical examination, n=6
Missing data for individual variables, n=50
Participants with complete data for all variables included in our analyses, n=3157

FIGURE 1 Flowchart of individuals targeted, invited, and finally included in our analyses. C1, sample 1 with a recruitment having started in 2004; C2, sample 2 with a recruitment having started in 2009; C3, sample 3 with a recruitment having started in 2014; N, total number of participants in the Lc65+; n, number of individuals.[39]

Table 3 shows that mean systolic BP and mean diastolic BP was lower in women than in men. While mean systolic BP tended to be higher in higher age categories, mean diastolic BP tended to be lower in higher age categories. Mean systolic BP and mean diastolic BP were lowest in frail participants and highest in non-frail participants. These differences in BP by frailty status were observed consistently across all sex and age categories of participants.

Table 4 shows that, compared to non-frail participants, mean age- and sex-adjusted systolic BP was lower by 2.7 mm Hg (95% confidence interval (CI): 1.4-4.1) and 6.7 mm Hg (95% CI: 3.2-10.3) among pre-frail and frail participants, respectively. Compared to non-frail participants, mean age- and sex-adjusted diastolic BP was lower by 1.9 mm Hg (95% CI: 1.1-2.8) and 4.9 mm Hg (95% CI: 2.8-7.0) in pre-frail and frail participants, respectively (model 1). Upon adjustment for socio-economic characteristics, CVD risk factors, and BMI, BP remained lower among pre-frail and frail participants compared to non-frail (model 2). With additional adjustment for antihypertensive treatment (model 3), the difference in BP between non-frail, pre-frail, and frail participants remained similar.

Sensitivity analyses with age included as a simple or quadratic continuous variable did not modify our findings. In further sensitivity analyses, we have tested for interactions between frailty and sex, age categories, hypercholesterolemia, diabetes, history of CVD, and smoking, respectively. None of these terms was statistically significantly associated with BP. Further, including these terms in the regression models did not modify our findings.

4 | DISCUSSION

Using data from a population-based study of older adults, we found that BP was lower among pre-frail and even lower among frail compared to non-frail individuals. This difference in BP was not explained by the greater use of antihypertensive treatment among frail or pre-frail older adults. Because low BP could be detrimental among frail older adults, these findings raise questions about hypertension management in this population and stress the need for additional evidence.

Our results are consistent with other studies having shown that a diagnosis of hypertension was more frequent in frail than in non-frail individuals (Table 2), but that measured mean BP was lower in frail compared to non-frail individuals (Table 3).[9] For instance, in a cohort study by Aprahamian et al in 2018, the prevalence of hypertension among non-frail, pre-frail, and frail individuals was 52%, 73%, and 83%, respectively.[25] With regard to BP, in one recent cross-sectional study by Gijón-Conde et al conducted among 1047 participants aged 60 years and over, mean systolic BP was significantly lower by 1.5 mm Hg per additional frailty category as measured by the frailty phenotype.[26] Other studies have been conducted using the frailty index based on the deficit accumulation model.[27] In one of these studies using electronic health records from 1.4 million people in the United Kingdom,[9] frailty was associated with low BP. In two other studies using cohort data from Canada and Korea, frailty was associated with a U-shaped BP curve.[27,28] Our study is based on high-quality data on BP and frailty and is, to our knowledge, the largest population-based study, which investigated the relationship between the frailty phenotype and BP. Although the frailty index may have a better ability to discriminate health risk in individuals, the frailty phenotype has a better clinical appeal, as the five criteria can be measured in clinical practice and interventions targeted on these features are possible.[29] This proximity to clinical practice is important in the context of decision-making on hypertension management.

Our study has several limitations. First, our sample included a relatively small number of frail individuals (n = 121; 3.3% of the total sample). Second, although we adjusted our regression models for age, sex, history of CVD, BMI, socio-economic characteristics, and antihypertensive medication use, there might be some residual confounding. A potential confounder could be diet for instance. Third, we rely on self-reported data to some extent, for example, data on hypertension diagnosis and antihypertensive medication use, and these data are less reliable than physical measurements. It is possible that some patients reporting antihypertensive medication use were actually taking them for other reasons than hypertension (eg, heart failure), leading to a potential overestimation of the proportion of hypertension in this population. Furthermore, we had no detailed information on the type of antihypertensive medication. The participants were asked whether they use antihypertensive medication, without other specifications. Last, our analytical sample may be subject to some selection bias. As shown in Figure 1, out of the 4731 participants initially recruited, 3157 were finally included in our analyses. Between recruitment and last data collection, 381 died and 569 left the study. From those who participated at the most recent data collection, 394 were excluded from the analytical sample due to missing data, mainly in BP measurements (Table 1). In most cases, these participants could not, or were not willing to, attend the physical examination. Since some frail older adults may have not participated, it is possible that the proportion of frail individuals in our sample is an underestimation of the true proportion in the source population of this age. For the same reason, the association between frailty and BP may be systematically different in these individuals, because withdrawing from the study may be associated with both frailty and low BP. Nevertheless, there was no major difference between participants with or without missing data (see Table S3 in the Supporting Information).

An important strength of our study is the high quality of data, especially regarding frailty and BP. The Lausanne cohort Lc65+ has been specifically designed to assess the development and determinants of frailty and, hence, frailty status has been carefully measured. Both BP and frailty have been measured for study purposes at the

TABLE 1 Baseline characteristics of participants at most recent data collection in the Lausanne cohort Lc65+

Characteristics of participants	n (%)
Total N	3651
Sex	
Women	2157 (59.1)
Men	1494 (40.9)
Missing	0 (0.0)
Age [years], mean (SD)	73.3 (4.1)
Missing, n(%)	0 (0.0)
Socio-economic characteristics	
Living alone	2364 (64.8)
Swiss citizenship	3223 (88.3)
Education	
Basic compulsory	645 (17.7)
Apprenticeship	1410 (38.6)
High school	902 (24.7)
University	675 (18.5)
Financial difficulties	938 (25.7)
Missing in at least one variable in socio-economic characteristics	419 (11.5)
Frailty status	
Non-frail	2226 (61.0)
Pre-frail	1243 (34.1)
Frail	121 (3.3)
Missing	61 (1.7)
BP [mm Hg], mean (SD)	
Systolic BP	135.1 (18.5)
Diastolic BP	76.3 (11.0)
Missing, n (%)	441 (12.1)
Hypertension	
Hypertension treatment or diagnosis (self-reported)	1867 (51.1)
Missing	37 (1.0)
Hypertension treatment (self-reported)	1601 (43.9)
Missing	51 (1.4)
BP ≥ 140/90 mm Hg (measured)	1248 (34.2)
Missing	441 (12.1)
BP ≥ 140/90 mm Hg (measured) or antihypertensive medication use (self-reported)	2243 (61.4)
Missing	248 (6.8)
Other CVD risk factors	
Hypercholesterolemia	1298 (35.6)
Diabetes	417 (11.4)
History of CVD	945 (25.9)
Smoking	
Current smoker	604 (16.5)
Former smoker	1468 (40.2)
Never smoker	1553 (42.5)
Missing in at least one variable in other CVD risk factors	79 (2.2)
BMI [kg/m2], mean (SD)	26.9 (4.8)
Missing, n (%)	442 (12.1)
BMI category	
Underweight (BMI < 18.5 kg/m^2)	48 (1.3)
Normal (BMI 18.5-24.9 kg/m^2)	1144 (31.3)
Overweight (BMI 25-29.9 kg/m^2)	1305 (35.7)
Obese (BMI ≥ 30 kg/m^2)	712 (19.5)
Missing	442 (12.1)
Number of chronic diseases	
0	746 (20.4)
1	1092 (29.9)
≥2	1813 (49.7)
Functional status	
Help received with BADLs	
No difficulties	2920 (80.0)
Difficulties	375 (10.3)
Difficulties and receiving help	113 (3.1)
Missing	243 (6.7)
Help received with IADLs	
No difficulties	2773 (76.0)
Difficulties	321 (8.8)
Difficulties and receiving help	373 (10.2)
Missing	184 (5.0)
Polypharmacy	751 (20.6)
Missing	435 (11.9)

Note: Values are numbers (%) unless indicated otherwise.
Polypharmacy: self-reported use of ≥5 medication at least once a week.
Abbreviations: BADL, basic activities of daily living; BP, blood pressure; CVD, cardiovascular disease; IADL, instrumental activities of daily living; n, number of participants; SD, standard deviation.

study center by trained study research assistants following a standardized procedure kept identical across years.[16] BP has been measured three times at one visit, although not using home or ambulatory BP monitoring, but nonetheless in line with an ideal clinical setting, with participants in a resting state and sitting in a recommended posture.[4,30] Another strength of our study is that we used the frailty phenotype, and not the frailty index; the frailty phenotype, although less discriminative, is more appealing for clinical use.[29] In fine, the external validity of our findings may be challenged by selection bias and reduced representativeness, and our results have a high internal validity due to reliable measurement methods for BP and frailty.

Our results suggest that an association between frailty and low BP exists, although the nature of this relationship stays unclear.[1] According to Hernán and Robins,[31] there are three structural reasons, why two variables may be associated: one variable is the

TABLE 2 Number (%) of participants with hypertension, and using antihypertensive medication, stratified by sex, age, and frailty status

		Men (n = 1299)				Women (n = 1858)				Men and women
		67-70 years	71-75 years	76-80 years	All age categories	67-70 years	71-75 years	76-80 years	All age categories	All age categories
Diagnosed with or treated for hypertension	Non-frail	164 (50.1)	118 (51.5)	165 (56.5)	447 (52.7)	134 (32.5)	124 (38.5)	179 (46.9)	437 (39.2)	884 (45.0)
	Pre-frail	81 (66.4)	79 (62.7)	112 (66.7)	272 (65.4)	86 (49.1)	93 (52.0)	191 (60.4)	370 (55.2)	642 (59.1)
	Frail	7 (70.0)	5 (83.3)	18 (94.7)	30 (85.7)	12 (70.6)	11 (52.4)	20 (58.8)	43 (59.7)	73 (68.2)
Treated for hypertension	Non-frail	137 (41.9)	104 (45.4)	150 (51.4)	391 (46.1)	110 (26.7)	106 (32.9)	162 (42.4)	378 (33.9)	769 (39.2)
	Pre-frail	71 (58.2)	71 (56.3)	99 (58.9)	241 (57.9)	68 (38.9)	79 (44.1)	172 (54.4)	319 (47.6)	560 (51.6)
	Frail	6 (60.0)	4 (66.7)	15 (79.0)	25 (71.4)	11 (64.7)	7 (33.3)	13 (38.2)	31 (43.1)	56 (52.3)

Note: The analytical sample consisted of 3157 participants with complete data for all variables. n, number of participants.

TABLE 3 Mean (SD) systolic and diastolic BP, stratified by sex, age, and frailty status

		Men (n = 1299)				Women (n = 1858)				Men and women
		67-70 y	71-75 y	76-80 y	All age categories	67-70 y	71-75 y	76-80 y	All age categories	All age categories
Systolic BP [mm Hg]	Non-frail	139.1 (16.0)	138.9 (17.6)	140.2 (17.7)	139.4 (17.0)	131.2 (18.9)	133.0 (17.8)	137.4 (19.7)	133.9 (19.1)	136.3 (18.4)
	Pre-frail	139.2 (19.3)	136.0 (15.6)	136.8 (18.3)	137.3 (17.9)	130.0 (19.3)	129.1 (16.5)	133.1 (18.1)	131.2 (18.1)	133.4 (18.2)
	Frail	134.1 (18.3)	130.8 (18.7)	131.4 (23.8)	132.1 (21.0)	126.8 (22.5)	128.5 (12.9)	128.4 (16.6)	128.1 (17.0)	129.1 (18.5)
Diastolic BP [mm Hg]	Non-frail	80.4 (10.8)	77.7 (10.5)	76.5 (10.8)	78.3 (10.9)	77.4 (10.6)	75.8 (9.9)	76.1 (10.6)	76.5 (10.5)	77.3 (10.7)
	Pre-frail	77.5 (11.1)	75.1 (9.8)	74.4 (11.1)	75.6 (10.8)	77.0 (12.0)	73.5 (10.5)	74.0 (11.0)	74.7 (11.2)	74.9 (11.1)
	Frail	77.3 (10.8)	73.9 (16.7)	64.6 (13.0)	69.8 (14.0)	73.6 (14.6)	75.0 (12.6)	71.2 (10.9)	72.9 (12.3)	71.6 (12.8)

Note: The analytical sample consisted of 3157 participants with complete data for all variables
Abbreviations: BP, blood pressure; n, number of participants; SD, standard deviation.

TABLE 4 Linear regression models of frailty upon systolic blood pressure (BP) and of frailty upon diastolic BP

	Model 1	Model 2	Model 3
	Difference in BP (95% CI) [mm Hg]	Difference in BP (95% CI) [mm Hg]	Difference in BP (95% CI) [mm Hg]
Systolic BP			
Frailty status			
Non-frail	Ref	Ref	Ref
Pre-frail	−2.7 (−4.1 to −1.4)	−2.6 (−3.9 to −1.2)	−2.8 (−4.2 to −1.5)
Frail	−6.7 (−10.3 to −3.2)	−6.1 (−9.6 to −2.5)	−6.2 (−9.8 to −2.7)
Age (y)			
67-70	Ref	Ref	Ref
71-75	0.1 (−1.5 to 1.7)	0.5 (−1.2 to 2.2)	0.4 (−1.3 to 2.0)
76-80	2.9 (1.4 to 4.4)	3.5 (1.8 to 5.2)	3.0 (1.3 to 4.7)
Sex			
Men	Ref	Ref	Ref
Women	−5.7 (−7.0 to −4.4)	−6.8 (−8.2 to −5.4)	−6.6 (−8.0 to −5.2)
BMI category			
Underweight	—	2.2 (−3.1 to 7.4)	2.5 (−2.7 to 7.7)
Normal weight	—	Ref	Ref
Overweight	—	3.0 (1.5 to 4.4)	2.4 (0.9 to 3.9)
Obese	—	1.6 (−0.2 to 3.4)	0.5 (−1.3 to 2.3)
Antihypertensive treatment			
No	—	—	Ref
Yes	—	—	4.4 (3.0 to 5.8)
Diastolic BP			
Frailty status			
Non-frail	Ref	Ref	Ref
Pre-frail	−1.9 (−2.8 to −1.1)	−1.8 (−2.6 to −1.0)	−1.8 (−2.7 to −1.0)
Frail	−4.9 (−7.0 to −2.8)	−4.4 (−6.5 to −2.3)	−4.4 (−6.5 to −2.3)
Age (y)			
67-70	Ref	Ref	Ref
71-75	−2.3 (−3.2 to −1.3)	−1.7 (−2.7 to −0.7)	—1.8 (−2.8 to −0.8)
76-80	−2.7 (−3.6 to −1.8)	−1.7 (−2.7 to −0.7)	−1.8 (−2.8 to −0.8)
Sex			
Men	Ref	Ref	Ref
Women	−1.3 (−2.1 to −0.5)	−2.0 (−2.9 to −1.2)	−2.0 (−2.8 to −1.2)
BMI category			
Underweight	—	0.4 (−2.7 to 3.4)	0.4 (−2.7 to 3.5)
Normal weight	—	Ref	Ref
Overweight	—	2.8 (1.9 to 3.7)	2.8 (1.9 to 3.6)
Obese	—	3.7 (2.6 to 4.7)	3.6 (2.5 to 4.7)
Antihypertensive treatment			
No	—	—	Ref
Yes	—	—	0.3 (−0.5 to 1.1)

Note: Coefficients are differences in mean blood pressure (BP) as compared to the reference category (ref). The analytical sample consisted of 3157 participants with complete data for all variables. Model 1: adjusted for age and sex. Model 2: Model 1+ adjusted for socio-economic characteristics (education, Swiss citizenship, financial difficulties, living alone), CVD risk factors (hypercholesterolemia, diabetes, history of CVD, smoking), and body mass index (BMI); Model 3: Model 2+ adjusted for antihypertensive medication use.
Abbreviation: 95% CI, 95% confidence interval.

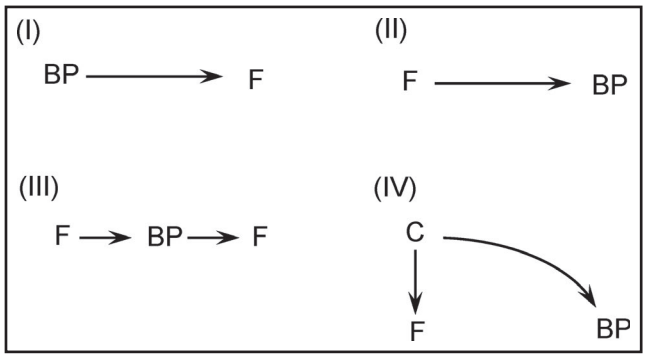

FIGURE 2 Potential causal relationships explaining the association between blood pressure (BP) and frailty (F). C, confounding factor

cause of the other, both variables share a common cause, or the association was analyzed while conditioning on a common effect of both variables. Figure 2 summarizes some hypotheses related to the previously mentioned reasons for an association. First, low BP may cause frailty (I). For instance, Muller et al speculated that low BP causes frailty in older individuals because, in a physiologically vulnerable state, low BP may reduce blood perfusion and oxygenation of vital organs, and, hence, lead to damage, loss of functionality, and a state of frailty.[32] Second, frailty may cause low BP (II). Indeed, a state of frailty is associated with a weakening of several physiological functions, including the ability of the heart to sustain a given level of BP. Third, frailty may cause low BP, which in turn could exacerbate frailty (III). Forth, the relationship might be due to confounding (IV). For instance, poor nutrition or some debilitating diseases can cause both frailty and a low BP.[9] The key is that confounding should be correctly assessed, using subject matter knowledge and integrating reflections on temporality, with some variables, for instance antihypertensive medications, acting as confounders at some time points and as mediators at some other time points. For these type of analyses, longitudinal data are needed, allowing the investigation of the effect of certain BP levels, but also of lifelong exposure to hypertension or to dynamic changes in BP as in end-of-life decline in BP.[9,33] Finally, we cannot exclude the possibility that selection bias explains part of our findings. Further studies are needed to understand the possible mechanisms at play.

Currently, hypertension management in older adults is still highly debated. This is well illustrated by discordances across current major hypertension management guidelines. Recent North American guidelines recommend treating older adults to systolic BP targets of 130 mm Hg, irrespective of older age or frailty status.[4] These recommendations have triggered criticism for downplaying and ignoring risks associated with low BP, such as falls, and physical and mental decline pinpointed in population-based cohort studies.[10,34] More conservative, European guidelines published in 2018 emphasize that BP thresholds and BP treatment targets should be set accounting for biological age, and that frailty, independence, and tolerability of treatment have to be considered in the decision on how to treat a patient. According to the latter, older age, however, is not an argument for denying treatment per se. These guidelines recommend to lower systolic BP in older adults below 140 mm Hg but not below 130 mm Hg.[5]

Key in the debate is to understand the relationship between BP and frailty. In addition to being associated with low BP, frailty has been shown to be associated with a higher risk for orthostatic hypotension[35,36] while the link with CVD risk remains unclear.[12,32,37] Since frail persons with multimorbidity and polypharmacy are highly prevalent and represent an ever-growing population in our aging society, there is an urgent need to clarify this relationship to enable healthcare providers to adequately manage hypertension. While opinions diverge, with some authors speculating that lowering BP in frail patients is harmful and others who consider frailty as a risk factor for undertreatment, there is a need for scientific evidence in frail participants.[4,5,38] An analysis using longitudinal data and aiming for causal inference may help understanding the relationship between BP and frailty and give an indication on how to treat frail older adults for hypertension.

In conclusion, our results show that BP and frailty occur together in older adults, and raise the question on why they are related and on what is the impact of this relationship on the management of hypertension in older adults.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

DA and AC had access to the data and take responsibility for the accuracy of the data analysis. DA and AC had the final responsibility for the decision to submit for publication. DA, BSE, AC involved in concept and design. DA, BSE, MZ, VS, NR, CW, AC involved in acquisition, analysis, or interpretation of data. DA and AC drafted the manuscript. DA, BSE, MZ, VS, NR, CW, and AC involved in critical revision of the manuscript for important intellectual content. DA, BSE, and MZ involved in administrative, technical, or material support. AC involved in supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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