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Blood pressure status, trajectories, and cardiovascular disease: the CoLaus|PsyCoLaus prospective study

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Département de Médecine
Service de Médecine Interne

Blood pressure status, trajectories, and cardiovascular disease: the CoLaus|PsyCoLaus prospective study

THESE

préparée sous la direction du Professeur Pedro Marques-Vidal
avec la co-direction du Professeur Julien Vaucher

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Médecin diplômé de la Confédération Suisse
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Blood pressure status, trajectories, and cardiovascular disease: the CoLaus|PsyCoLaus prospective study

sans se prononcer sur les opinions exprimées dans cette thèse.

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Blood pressure status, trajectories, and cardiovascular disease: the CoLaus|PsyCoLaus prospective study

Statut et trajectoires de pression artérielle et maladie cardiovasculaire: l'étude prospective CoLaus|PsyCoLaus

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RÉSUMÉ

Contexte : L'hypertension artérielle (HTA) est un facteur de risque majeur de maladies cardiovasculaires (MCV). Un traitement adéquat de l'HTA devrait réduire le risque de MCV, mais cette association a rarement été évaluée dans un cadre de population générale.

Méthodes : Étude prospective populationnelle menée à Lausanne, en Suisse, avec un suivi entre 2003 et 2021. Les participants ont été catégorisés en tant que tension artérielle normale, HTA non traitée, HTA traitée non contrôlée et HTA traitée contrôlée. La mortalité totale et liée aux MCV ainsi que tout événement cardiovasculaire ont été évalués.

Résultats : 5 341 participants (65 % avec une tension artérielle normale, 17,4 % non traités, 8,8 % traités et non contrôlés et 8,8 % traités et contrôlés) ont été inclus. Après un suivi médian de 14 ans [intervalle interquartile : 11-15], 575 événements cardiovasculaires se sont produits. Par rapport aux participants ayant une tension artérielle normale, les risques relatifs (RR) ajustés et leurs intervalles de confiance à 95 % pour les MCV étaient de 1,38 (1,11-1,72) pour les non traités, 1,35 (1,04-1,76) pour les traités et non contrôlés, et 1,50 (1,15-1,95) pour les traités et contrôlés. Les RR correspondants pour la mortalité due aux MCV (112 événements) étaient de 0,94 (0,52-1,70), 1,77 (1,00-3,12) et 2,52 (1,50-4,23), respectivement. Pour la mortalité totale (677 événements), les RR étaient de 1,24 (1,01-1,52), 1,26 (0,99-1,60) et 1,27 (0,99-1,62), respectivement. Une analyse de sensibilité utilisant le statut tensionnel pendant une période de 5 ans et classant les participants comme toujours normaux, toujours traités non contrôlés, toujours traités contrôlés et autres a conduit à des résultats similaires.

Conclusion : Sur une période de suivi de 14 ans, le contrôle de la tension artérielle n'était pas associé à une réduction des événements cardiovasculaires, de la mortalité liée aux MCV ou de la mortalité totale. Cette constatation devrait aider à définir de nouvelles études sur les facteurs affectant les MCV et la mortalité chez les personnes traitées pour l'hypertension dans la population générale.

openheart

Blood pressure status, trajectories and cardiovascular disease: the CoLaus | PsyCoLaus prospective study

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ABSTRACT

Background High blood pressure (BP) is a major risk factor for cardiovascular disease (CVD). Adequate treatment of high BP should reduce the risk of CVD, but this association has seldom been assessed in a general population setting.

Methods Population-based prospective study conducted in Lausanne, Switzerland, with a follow-up between 2003 and 2021. Participants were categorised as normal BP, untreated high BP, treated and uncontrolled BP and treated and controlled BP. Total and CVD mortality as well as any CVD event were assessed.

Results 5341 participants (65% normal, 17.4% untreated, 8.8% treated and uncontrolled and 8.8% treated and controlled) were included. After a median follow-up of 14 years (IQR: 11–15), 575 CVD events occurred. Relative to participants with normal BP, multivariable-adjusted HRs (and 95% CI) for total CVD were 1.38 (1.11 to 1.72) for untreated, 1.35 (1.04 to 1.76) for treated and uncontrolled and 1.50 (1.15 to 1.95) for treated and controlled. The corresponding HRs for CVD mortality (112 events) were 0.94 (0.52 to 1.70), 1.77 (1.00 to 3.12) and 2.52 (1.50 to 4.23), respectively. For total mortality (677 events), the HRs were 1.24 (1.01 to 1.52), 1.26 (0.99 to 1.60) and 1.27 (0.99 to 1.62), respectively. Sensitivity analysis using BP status during a 5-year period and categorising participants as always normal, always treated and uncontrolled, always treated and controlled and other led to similar findings.

Conclusion Over a long follow-up period of 14 years, BP control was not associated with reduction of CVD events, CVD-related or total mortality. This finding should help define further studies on factors affecting CVD and mortality in people treated for hypertension in the general population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hypertension is a major preventable cause of cardiovascular disease (CVD), which is the first cause of death globally.
⇒ Whether adequate management of high blood pressure (BP) levels over the years reduces CVD events and/or mortality in the general population remains an open debate.

WHAT THIS STUDY ADDS

⇒ This is one of the few population-based studies assessing the effect of BP status and BP trajectories on CVD events, CVD-related and all-cause mortality, with a long follow-up (up to 14 years).
⇒ Our study confirms that effective BP control remains suboptimal.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Management of hypertension per se appears to be insufficient to prevent CVD in the general population. A holistic approach on all CVD risk factors should be considered.

INTRODUCTION

Cardiovascular disease (CVD) is the first cause of death globally, accounting for over 17 million deaths annually.[1] Hypertension is a major preventable cause of CVD and all-cause death.[2] The global prevalence of hypertension was estimated to be 1.13 billion in 2015, with an estimated increase of 15%–20% by 2025.[2] Despite the substantial progresses that have been made in understanding the epidemiology and pathophysiology of hypertension and effective treatment strategies, blood pressure (BP) control remains suboptimal worldwide.[2–5] Evidence shows that lowering BP can substantially reduce premature morbidity and mortality,[2 6] but whether inadequate management of BP levels is better than the absence of management remains an open debate. Studies failed to show the benefits of controlled versus uncontrolled hypertension on survival,[7 8] whereas others suggested that treatment of hypertension could lead to worse prognosis than untreated hypertension.[8 9]

To investigate the role of BP control on cardiovascular outcomes and overall mortality in a general population with a long follow-up, we first aimed to assess the development of CVD according to BP status: normal, high untreated, treated and controlled, and treated and uncontrolled. Second, we assessed the development of CVD according

to a 5-year BP trajectory. Our hypothesis was that people treated and controlled for hypertension would present a lower incidence of cardiovascular outcomes and mortality than people untreated or treated and uncontrolled.

METHODS

Study setting

The CoLaus|PsyCoLaus study is a population-based study investigating the epidemiology and genetic determinants of psychiatric and CVD in Lausanne, Switzerland.[10] Briefly, a representative sample was collected through a simple, non-stratified random sampling of 19 830 individuals (35% of the source population) aged between 35 years and 75 years. The baseline study was conducted between June 2003 and May 2006; the first follow-up was performed between April 2009 and September 2012; the second follow-up was performed between May 2014 and April 2017, and the third follow-up was performed between April 2018 and May 2021. Median follow-up time was 5.4 (average 5.6, range 4.5–8.8) years for the first follow-up, 10.7 (average 10.9, range 8.8–13.6) years for the second follow-up and 14.5 (average 14.6, range 13.2–17.3) for the third follow-up.

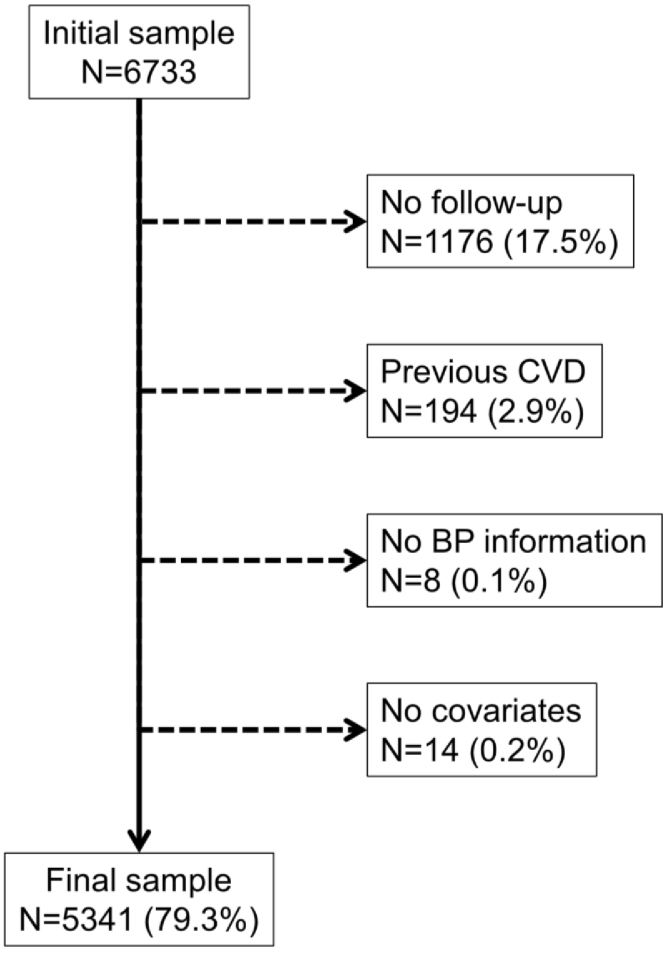

Figure 1 Selection of participants for the analysis between blood pressure at baseline and cardiovascular events and mortality, CoLaus study, Lausanne, Switzerland. BP, blood pressure; CVD, cardiovascular disease.

Blood pressure measurements and categorisation

BP was measured using an Omron HEM-907 (Kyoto, Japan) automated oscillometric sphygmomanometer after at least a 10 min rest in a seated position, and the average of the last two measurements was used. Hypertension was defined by systolic BP (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg or the presence of antihypertensive drug treatment.[2 3 11] Antihypertensive drug treatment was assessed by asking the participants if they took medication against hypertension and by checking their prescribed medicines. Control of hypertension was considered for participants treated for hypertension and presenting with SBP <140 mm Hg and DBP<90 mm Hg.

For the first aim, four groups were created according to the BP status at baseline: (1) normal, (2) treated and controlled, (3) treated and uncontrolled and (4) untreated.

For the second aim, four groups were created according to the BP status at baseline and the first follow-up (online supplemental table 1): (1) normal untreated at both evaluations, (2) treated and controlled at both evaluations, (3) treated and uncontrolled at both evaluations and (4) other.

Death and cardiovascular events

During the follow-up period, first incident CVD events and deaths were prospectively collected and independently adjudicated according to established recommendations and similar definitions detailed elsewhere.[12] Details of the adjudication procedure are provided in online supplemental annex 1.

Other covariates

Smoking was self-reported and categorised as never, former (irrespective of the time since quitting smoking) and current. Education was categorised into high (university), middle (high school) and low (apprenticeship + primary). Marital status was defined as living alone (single, divorced or widowed) or living with a partner. Nationality was defined as Swiss or other. All drugs reported by the participants were collected and coded according to the Anatomical Therapeutic Chemical (ATC) classification.

Participants reported whether they currently consumed alcohol and how many standard drinks they had consumed in the past 7 days. Participants were then categorised according to the number of drinks per week: non-drinkers (0 drinks/week), moderate (1–13 drinks/week) alcohol consumption, high (14–34 drinks/week) alcohol consumption and very high (≥35 drinks/week) alcohol consumption.[13 14]

Body weight and height were measured with participants barefoot and in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a seca scale (Hamburg, Germany). Height was measured to the nearest 5 mm using a seca (Hamburg, Germany)

Table 1 Baseline characteristics according to blood pressure status, CoLaus|PsyCoLaus study

	Normal	Treated and controlled	Treated and uncontrolled	Untreated	P value
N (%)	3474 (65.0)	469 (8.8)	469 (8.8)	929 (17.4)	
Age, years	49.6±9.8	59.7±9.3	61.3±9.0	56.7±10.2	<0.001
Women, %	2020 (58.2)	260 (55.4)	220 (46.9)	392 (42.2)	<0.001
Born in Switzerland (%)	2098 (60.4)	320 (68.2)	323 (68.9)	632 (68.0)	<0.001
Living with a partner (%)	2341 (67.4)	303 (64.6)	300 (64.0)	633 (68.1)	0.268
Educational level, %					<0.001
High	832 (24.0)	71 (15.2)	45 (9.6)	148 (15.9)	
Middle	926 (26.7)	93 (19.8)	103 (22.0)	224 (24.1)	
Low	1714 (49.4)	305 (65.0)	320 (68.4)	557 (60.0)	
BMI, kg/m^2, mean±SD	24.5±3.9	27.9±5.1	28.7±5.0	26.9±4.4	<0.001
BMI categories, %					<0.001
Normal	2098 (60.4)	144 (30.7)	108 (23.0)	332 (35.7)	
Overweight	1110 (32.0)	191 (40.7)	203 (43.3)	407 (43.8)	
Obese	266 (7.6)	134 (28.6)	158 (33.7)	190 (20.5)	
SBP, mm Hg, mean±SD	119±11	125±10	152±15	149±13	<0.001
DBP, mm Hg, mean±SD	75±8	76±8	90±10	91±9	<0.001
Smoking status, %					<0.001
Never	1416 (40.8)	190 (40.5)	200 (42.6)	370 (39.8)	
Former	1059 (30.5)	170 (36.3)	183 (39.1)	347 (37.4)	
Current	999 (28.7)	109 (23.2)	86 (18.3)	212 (22.8)	
Alcohol intake, %					<0.001
Non-drinkers	947 (27.3)	154 (32.8)	126 (26.8)	221 (23.8)	
Moderate (1–13/week)	2070 (59.6)	243 (51.8)	226 (48.2)	468 (50.4)	
High (14–34/week)	418 (12.0)	58 (12.4)	96 (20.5)	212 (22.8)	
Very high (≥35/week)	39 (1.1)	14 (3.0)	21 (4.5)	28 (3.0)	
Diagnosed diabetes, %	80 (2.3)	80 (17.1)	90 (19.2)	61 (6.6)	<0.001
Hypolipidemic drug, %	218 (6.3)	133 (28.4)	126 (26.9)	85 (9.2)	<0.001
Lipids, mmol/L					
Total cholesterol, mean±SD	5.52±1.01	5.48±1.03	5.68±0.99	5.89±1.01	<0.001
HDL cholesterol, mean±SD	1.68±0.44	1.54±0.42	1.57±0.44	1.63±0.46	<0.001
Triglycerides, median (IQR)	1.0 (0.7–1.4)	1.3 (0.9–1.8)	1.4 (1.0–2.0)	1.2 (0.9–1.8)	<0.001 §

Results are expressed as the number of participants (column percentage) for categorical variables and as mean±SD or median and IQR for continuous variables. Between groups, comparisons are performed using χ^2 for categorical variables and analysis of variance or Kruskal-Wallis test (§) for continuous variables.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

height gauge. Body mass index (BMI) was calculated and categorised as normal (<25 kg/m^2), overweight (≥25 kg/m^2 and <30 kg/m^2) and obese (≥30 kg/m^2).

Total cholesterol was assessed by CHOD-PAP, with maximum interbatch and intrabatch coefficient of variability (CVs) of 1.6% and 1.7%, respectively. High-density lipoprotein cholesterol was assessed by CHOD-PAP + polyethylene-glycol + cyclodextrin, with maximum interbatch and intrabatch CVs of 3.6% and 0.9%, respectively. Glucose was assessed by glucose dehydrogenase, with maximum interbatch and intrabatch CVs of 2.1% and 1.0%, respectively. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L and/or the presence of oral hypoglycaemic or insulin treatment. Hypolipidemic drug treatment was considered for any ATC code beginning with C10 (lipid-modifying agents).

Inclusion and exclusion criteria

For the first objective, participants were excluded if they (1) did not participate in the follow-up, (2) presented with previous CVD at baseline, (3) had missing data

regarding medicines and (4) had missing data for any covariate.

For the second objective, participants were excluded if they (1) did not participate in the follow-up, (2) presented with previous CVD at the first follow-up, (3) had missing data regarding medicines and (4) had missing data for any covariate.

Ethical statement

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch), approved the baseline CoLaus study (reference 16/03). The approval was renewed for the first (reference 33/09), the second (reference 26/14) and the third (reference PB_2018–0 00 408) follow-ups. The approval for the entire CoLaus|PsyCoLaus study was confirmed in 2021 (reference PB_2018–00038, 239/09). The full decisions of the CER-VD can be obtained from the authors on request. The study was performed in agreement with the Helsinki Declaration and its former amendments and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Statistical analysis

Statistical analyses were conducted using Stata V.16.1 (Stata Corp, College station, Texas, USA). Descriptive results were provided as the number of participants (percentage) for categorical variables and as average±SD or median (IQR) for continuous variables. Bivariate analyses were conducted using χ^2 for categorical variables and Student's t-test or Kruskal-Wallis test for continuous variables.

For both objectives, the association between BP categories and outcomes was assessed using Cox proportional hazard regression[15] for total mortality and Fine-Gray competing risk model for CVD, using non-cardiac mortality as competing event.[16] Results were expressed as HR and 95% CI. Multivariable analyses were adjusted for gender (man and woman), age (continuous), educational level (high, middle and low), smoking categories (never, former and current), BMI categories (normal, overweight and obese), alcohol consumption categories (non-drinkers, moderate, high and very high), diabetes (yes or no) and the presence of hypolipidemic drug treatment (yes or no).

As a sizeable fraction of the sample was excluded, we performed a sensitivity analysis using inverse probability weighting. Briefly, logistic regression was used to estimate the likelihood of being included for each participant using covariates that were significantly different between included and excluded participants. The inverse of the predicted probability was then used for the analysis of the associations between BP categories and outcomes.

Statistical significance was considered for a two-sided test with $p<0.05$.

Table 2 Prospective association between blood pressure control and cardiovascular events, CoLaus|PsyCoLaus study

	Person-years	Events	Incidence	Model 1	P value	Model 2	P value
Cardiovascular disease							
Normal	45 339.2	240	5.3 (4.7–6.0)	1 (ref)		1 (ref)	
Treated and controlled	5412.0	94	17.4 (14.2–21.3)	3.36 (2.65–4.27)	<0.001	1.50 (1.15–1.95)	0.002
Treated and uncontrolled	5253.8	95	18.1 (14.8–22.1)	3.52 (2.77–4.46)	<0.001	1.35 (1.04–1.76)	0.027
Untreated	11 113.4	146	13.1 (11.2–15.5)	2.55 (2.07–3.13)	<0.001	1.38 (1.11–1.72)	0.004
Cardiovascular death							
Normal	46 176.0	33	0.7 (0.5–1.0)	1 (ref)		1 (ref)	
Treated and controlled	5688.7	32	5.6 (4.0–8.0)	7.51 (4.62–12.2)	<0.001	2.52 (1.50–4.23)	<0.001
Treated and uncontrolled	5614.2	28	5.0 (3.4–7.2)	6.55 (3.98–10.8)	<0.001	1.77 (1.00–3.12)	0.050
Untreated	11 672.6	19	1.6 (1.0–2.6)	2.20 (1.25–3.87)	0.006	0.94 (0.52–1.70)	0.838
Overall mortality							
Normal	46 176.0	264	5.7 (5.1–6.5)	1 (ref)		1 (ref)	
Treated and controlled	5688.7	108	19.0 (15.7–22.9)	3.37 (2.70–4.22)	<0.001	1.27 (0.99–1.62)	0.056
Treated and uncontrolled	5614.2	128	22.8 (19.2–27.1)	4.02 (3.25–4.97)	<0.001	1.26 (0.99–1.60)	0.056
Untreated	11 672.6	177	15.2 (13.1–17.6)	2.75 (2.27–3.32)	<0.001	1.24 (1.01–1.52)	0.040

Results are expressed as value (95% CI). Model 1: unadjusted. Model 2: adjusted for gender, age in decades, born in Switzerland (yes or no), educational level (high, middle and low), marital status (living with a partner and living alone), smoking categories (never, former and current), BMI categories (normal, overweight and obese), alcohol consumption categories (none, low, medium-high and very high), diabetes (yes or no) and hypolipidemic drug treatment (yes or no). Statistical analysis using Cox model for overall mortality and CVD events and Fine-Gray model using non-CVD death as a competing event for CVD mortality.

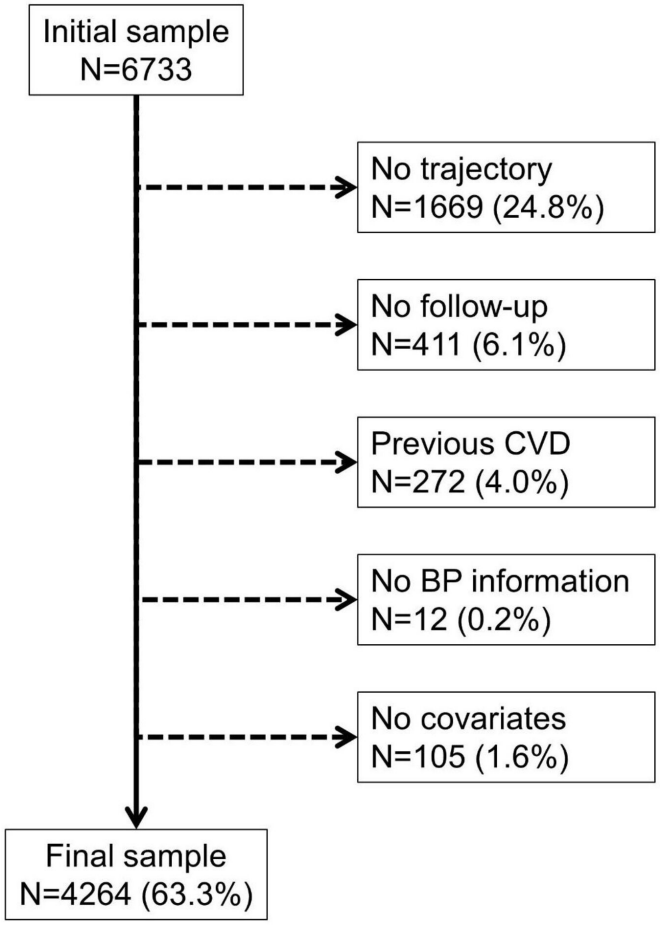

Figure 2 Selection of participants for the analysis between blood pressure trajectories and cardiovascular events and mortality, CoLaus study, Lausanne, Switzerland. BP, blood pressure; CVD, cardiovascular disease.

RESULTS

Blood pressure status and events: participant selection and characterisation

Of the initial 6733 participants, 5341 (79.3%) were included. The reasons for exclusion are presented in figure 1, and the comparison between included and excluded participants is provided in online supplemental table 2. Included participants were more frequently women, had a higher educational level, had a lower prevalence of obesity, were less frequently non-drinkers and presented less frequently with diabetes than excluded participants.

The characteristics of the participants according to BP status at baseline is presented in table 1. Participants with treated or untreated hypertension represented 35% of the sample. Among participants with hypertension, 49.8% were untreated, and among those treated, 50% were controlled. The four groups differed regarding age, gender distribution, educational level, BMI categories, smoking status, the prevalence of diabetes and hypolipidemic drugs, and lipid levels (table 1).

Blood pressure status and events: bivariate and multivariable analyses

After a median follow-up of 14 years (IQR: 11–15), 575 CVD events (112 deaths) and 677 all-cause deaths occurred. The bivariate and multivariable associations between BP control and incidence of cardiovascular events and overall mortality are summarised in table 2. Compared with participants with normal, untreated BP levels, participants with treated or untreated hypertension had a higher risk of cardiovascular events, participants treated for hypertension had a higher risk of cardiovascular death irrespective of their control status and participants with untreated hypertension had a higher risk of death from all causes (table 2).

Similar findings were obtained after inverse probability weighting, except that participants with treated and uncontrolled hypertension had a higher risk of death from all causes, while the association for participants with untreated hypertension was no longer statistically significant (online supplemental table 3).

Blood pressure trajectories and events: participant selection and characterisation

Of the initial 6733 participants at baseline, 4264 (63.3%) were included in the analysis between BP trajectories and events. The reasons for exclusion are indicated in figure 2, and the comparison between included and excluded participants is provided in online supplemental table 4. Included participants were younger, more frequently women, of higher education, more frequently born in Switzerland, of normal weight, never smokers, low-risk drinkers and presented less frequently with diabetes.

Most participants (56.3%) had consistently normal BP levels throughout the study period ('always normal' group). A small percentage (4.6%) had consistently treated and controlled BP, and a similar percentage (4.1%) had consistently treated but uncontrolled BP. The remaining participants (35.0%) fell into the 'other' category. Their clinical characteristics are summarised in table 3. Significant differences were observed across the BP trajectory groups: participants whose BP levels were always normal were younger, more frequently women, of higher education, more frequently of normal weight, current smokers, moderate-risk or high-risk drinkers and presented less frequently with diabetes or with hypolipidemic drug treatment.

Blood pressure trajectories and events: bivariate and multivariable analyses

The bivariate and multivariable associations between BP trajectories and incidence of cardiovascular events and overall mortality are summarised in table 4.

After a median follow-up time of 9 years (IQR: 7–9.2), 325 CVD events (52 deaths) and 321 all-cause deaths occurred. On bivariate analysis, compared with participants with consistently normal BP levels, those in the 'always treated and controlled', 'always treated and uncontrolled' and 'other' groups exhibited higher

Table 3 Participants' characteristics at the first follow-up according to blood pressure trajectories, CoLaus|PsyCoLaus study

	Always normal	Always treated and controlled	Always treated and uncontrolled	Other	P value
N (%)	2401	195	175	1493	
Age, years	53.7±9.0	63.7±9.5	66.9±9.0	61.4±10.2	<0.001
Women, %	1452 (60.5)	108 (55.4)	87 (49.7)	704 (47.2)	<0.001
Born in Switzerland (%)	1470 (61.2)	132 (67.7)	118 (67.4)	995 (66.6)	0.002
Living with a partner (%)	1367 (56.9)	101 (51.8)	96 (54.9)	878 (58.8)	0.225
Educational level, %					<0.001
High	631 (26.3)	33 (16.9)	14 (8.0)	267 (17.9)	
Middle	667 (27.8)	40 (20.5)	45 (25.7)	384 (25.7)	
Low	1101 (45.9)	122 (62.6)	116 (66.3)	841 (56.4)	
BMI, kg/m^2, mean±SD	24.8±3.9	28.3±5.0	28.5±5.3	27.4±4.7	<0.001
BMI categories, %					<0.001
Normal	1363 (56.8)	49 (25.1)	42 (24.0)	469 (31.4)	
Overweight	828 (34.5)	86 (44.1)	73 (41.7)	657 (44.0)	
Obese	210 (8.8)	60 (30.8)	60 (34.3)	367 (24.6)	
SBP, mm Hg, mean±SD	116±11	123±11	153±14	138±16	<0.001
DBP, mm Hg, mean±SD	74±8	75±8	88±11	85±11	<0.001
Smoking status, %					<0.001
Never	1003 (41.8)	82 (42.0)	76 (43.4)	614 (41.1)	
Former	804 (33.5)	78 (40.0)	77 (44.0)	629 (42.2)	
Current	594 (24.7)	35 (18.0)	22 (12.6)	250 (16.7)	
Alcohol intake, %					<0.001
Non-drinkers	556 (23.2)	54 (27.7)	48 (27.4)	556 (23.2)	
Moderate (1–13/week)	1542 (64.2)	125 (64.1)	89 (50.9)	1542 (64.2)	
High (14–34/w)	285 (11.9)	14 (7.2)	31 (17.7)	285 (11.9)	
Very high (35+/week)	18 (0.8)	2 (1.0)	7 (4.0)	18 (0.8)	
Diagnosed diabetes, %	97 (4.0)	47 (24.1)	41 (23.4)	228 (15.3)	<0.001
Hypolipidemic drug, %	251 (10.5)	78 (40.0)	51 (29.1)	384 (25.7)	<0.001
Lipids, mmol/L					
Total cholesterol, mean±SD	5.75±0.99	5.44±1.09	5.76±1.01	5.77±1.03	<0.001
HDL cholesterol, mean±SD	1.70±0.47	1.50±0.42	1.59±0.43	1.61±0.47	<0.001
Triglycerides, median (IQR)	1.0 (0.7–1.4)	1.3 (0.9–1.8)	1.4 (1.0–2.0)	1.2 (0.9–1.8)	<0.001 §

Results are expressed as the number of participants (column percentage) for categorical variables and as mean±SD or median and IQR for continuous variables. Between groups, comparisons are performed using χ^2 for categorical variables and analysis of variance or Kruskal-Wallis test (§) for continuous variables.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

incidence rates of cardiovascular events, cardiovascular death and overall mortality. After adjusting for potential confounding factors, the associations remained consistent, although not reaching statistical significance. Still, there was a trend towards higher incidence rates for all events in participants with consistently treated and uncontrolled BP, as well as in those classified in the 'other' category (see table 4). Further analysis performed using inverse probability weighting to account for excluded participants led to similar findings (see online supplemental table 5).

DISCUSSION

The present study investigated the development of CVD and mortality in people according to their BP status and 5-year BP trajectory. People with hypertension had a significantly higher risk of developing CVD and CVD-related mortality that was not mitigated by antihypertensive drug treatment. Our findings also suggest that participants belonging to the 'always treated and uncontrolled' BP trajectory may experience a worse prognosis in terms of CVD, CVD-related death and overall mortality.

Table 4 Association between blood pressure trajectories and cardiovascular events, CoLaus|PsyCoLaus study

	Person-years	Events	Incidence	Model 1	P value	Model 2	P value
Cardiovascular disease							
Always normal	19578.2	111	5.7 (4.7–6.8)	1 (ref)		1 (ref)	
Always treated and controlled	1466.0	20	13.6 (8.8–21.1)	2.42 (1.50–3.90)	<0.001	0.94 (0.57–1.55)	0.811
Always treated and uncontrolled	1193.6	25	20.9 (14.2–31.0)	3.76 (2.43–5.80)	<0.001	1.21 (0.76–1.94)	0.416
Other	11171.6	165	14.8 (12.7–17.2)	2.63 (2.07–3.35)	<0.001	1.24 (0.95–1.62)	0.117
Cardiovascular death							
Always normal	19840.4	9	0.5 (0.2–0.9)	1 (ref)		1 (ref)	
Always treated and controlled	1521.0	7	4.6 (2.2–9.7)	9.60 (3.56–25.9)	<0.001	2.12 (0.77–5.83)	0.145
Always treated and uncontrolled	1251.5	8	6.4 (3.2–12.8)	13.1 (5.03–34.0)	<0.001	2.20 (0.80–6.07)	0.126
Other	11575.9	28	2.4 (1.7–3.5)	5.14 (2.43–10.9)	<0.001	1.48 (0.67–3.27)	0.326
Overall mortality							
Always normal	19840.4	95	4.8 (3.9–5.9)	1 (ref)		1 (ref)	
Always treated and controlled	1521.0	31	20.4 (14.3–29.0)	4.00 (2.65–6.06)	<0.001	1.16 (0.75–1.80)	0.496
Always treated and uncontrolled	1251.5	31	24.8 (17.4–35.2)	5.20 (3.46–7.80)	<0.001	1.11 (0.71–1.72)	0.650
Other	11575.9	168	14.5 (12.5–16.9)	3.07 (2.39–3.95)	<0.001	1.10 (0.83–1.45)	0.516

Results are expressed as value (95% CI). Model 1: unadjusted. Model 2: adjusted for gender, age in decades, born in Switzerland (yes or no), educational level (high, middle and low), marital status (living with a partner and living alone), smoking categories (never, former and current), BMI categories (normal, overweight and obese), alcohol consumption categories (none, low, medium-high and very high), diabetes (yes and no) and hypolipidemic drug treatment (yes and no). Statistical analysis using Cox model for overall mortality and CVD events and Fine-Gray model using non-CVD death as a competing event for CVD mortality.

Blood pressure status and events

To our knowledge, our study is one of the few recent European investigations concerning persistent BP status and its association with CVD events. Our findings align with several previous studies (table 5). For instance, the study by Zhou *et al* in the USA found that participants with untreated or treated but uncontrolled hypertension had a higher risk of all-cause and CVD-related mortality compared with normotensive individuals.[15] In our study, participants in the treated and controlled group had a higher hazard rate than reported in the same group by Zhou *et al*.[15] A possible explanation might be the older age of our sample, as 56.9% were over 65 years old, versus 41.9% for the study of Zhou *et al*,[15] although other unmeasured factors might intervene. Conversely, the HR for overall mortality in this study tended to be comparable with those of Zhou *et al* and Barengo *et al*, suggesting a consistent impact of BP status on general mortality outcomes across these diverse populations.[15 17] Similarly, the study by Rojas *et al* in Cuba reported that participants with uncontrolled hypertension had an increased risk of all-cause and CVD-related mortality.[5] A possible explanation for the lack of a protective effect of BP control would be that participants took their treatment just before

Table 5 comparative overview of cardiovascular and overall mortality findings between the current study and two previously conducted investigations by Barengo *et al*[17] and Zhou *et al*[15]

	Barengo 2013	Zhou 2018	Current study
Cardiovascular death			
Normal	N/A	1 (ref)	1 (ref)
Treated and controlled	N/A	1.12 (0.76–1.63)	2.88 (1.65–5.04)
Treated and uncontrolled	N/A	2.23 (1.66–2.99)	1.93 (1.06–3.52)
Untreated	N/A	1.77 (1.34–2.35)	1.03 (0.56–1.93)
Overall mortality			
Normal	1 (ref)	1 (ref)	1 (ref)
Treated and controlled	0.86 (0.57–1.28)	1.14 (0.95–1.42)	1.23 (0.95–1.61)
Treated and uncontrolled	1.68 (1.45–1.94)	1.62 (1.35–1.95)	1.30 (1.02–1.66)
Untreated	1.32 (1.17–1.48)	1.40 (1.12–1.62)	1.22 (0.98–1.52)

Results are expressed as HR and 95% CIs

Table 6 Comparative overview of results between the current study and previous studies analysing blood pressure trajectories and CVD and mortality

Author, year	Country	Sample size	Categories	Results
German *et al*, 2021[24]	USA	8901	Group 1: BP low decline Group 2: BP high decline Group 3: BP low stable Group 4: BP high stable	Relative to group 1, group 4 showed 76% increased risk of all-cause mortality
Ravindrarajah *et al*, 2017[27]	UK	144 403	Group 1: slow decline in SBP Group 2: accelerated decline in SBP	Compared with group 1, group 2 had a higher risk of death
Li *et al*, 2017[28]	China	79 385	Group 1: normotensive stable Group 2: prehypertension stable Group 3: stage 1 hypertension increasing Group 4: stage 1 hypertension decreasing Group 5: stage 2 hypertension stable	Relative to group 1, groups 2 and 5 had a higher risk of stroke
Smitson *et al*, 2017[21]	USA	4067	Group 1: increase in SBP and DBP Group 2: stable SBP but declines in DBP Group 3: decline in both SBP and DBP	Relative to group 1, groups 2 and 3 had a higher risk of death
Portegies *et al*, 2016[29]	The Netherlands	6745	Group 1: BP small increase Group 2: BP steep increase Group 3: BP persistently high Group 4: BP decreasing	Relative to group 1, groups 2 and 4 had a higher risk of mortality, and all groups had a higher risk of stroke
Barengo *et al*, 2013[17]	Finland	26 133	Group 1: normotensive Group 2: hypertensive, treated, SBP and DBP controlled Group 3: hypertensive, treated, SBP controlled, DBP uncontrolled Group 4: hypertensive, treated, SBP uncontrolled, DBP controlled Group 5: hypertensive, treated, SBP and DBP uncontrolled Group 6: hypertensive, not treated	Relative to group 1, all groups except group 2 have increased all-cause mortality HRs are higher in group 3 (1.45), group 4 (1.48) and group 5 (1.61) compared with group 6 (1.26)
Current study	Switzerland	5341	Group 1: normotensive Group 2: hypertensive, treated, controlled Group 3: hypertensive, treated, uncontrolled Group 4: other	Although no significant association was found, relative to group 1, all groups showed a trend towards higher CVD death and all-cause mortality

coming to the clinical evaluation. Indeed, it has been shown that over one-fifth of patients temporarily discontinue their antihypertensive treatment which may have influenced our results.[18] Another possible explanation is that our categorisation regarding high BP or BP control was based on a single measurement, which might have led to some misclassification of participants due to the white coat hypertension phenomenon. Still, white-coat hypertension has been suggested to be associated with an increased risk of CVD, which would explain the higher CVD risk observed among untreated participants.[19] Interestingly, in elderly individuals, the relationship between BP and health outcomes is more complex. Anker *et al* demonstrated that low BP in frail older adults might be associated with worse health outcomes.[20] Smitson *et al* revealed that declining BP trajectories on elderly individuals were linked to an increased risk of mortality and higher rates of CVD.[21] This notion aligns with the findings from other studies that highlighted the potential risk of very low DBP, emphasising the importance of considering both SBP and DBP levels for optimal cardiovascular health.[22 23] Overall, these studies highlight the intricate relationship between BP, frailty and health outcomes in elderly patients, potentially elucidating the reasons behind our inability to demonstrate a protective effect of BP reduction.

Blood pressure trajectories and events

No significant association was found between BP trajectories and CVD or overall mortality. Several studies have explored the relationship between BP trajectories and cardiovascular outcomes, and no consensus could be found. The study by German *et al* used data from the Systolic Blood Pressure Intervention Trial to identify four distinct SBP trajectories.[24] The authors found that participants with uncontrolled BP levels had a worse prognosis regarding CVD events and all-cause mortality, irrespective of their baseline BP. A study by Smitson *et al* on US elderly identified three distinct BP trajectory groups, participants with declining BP trajectories presenting an increased mortality risk compared with those with stable or increasing trajectories.[21] Finally, the study by Barengo

et al observed a significant increase in all-cause mortality among treated hypertensive participants who had only their SBP or DBP controlled.[17] Overall, there is a lack of consensus regarding whether adequate management of high BP levels reduces CVD events in the general population, and it would be important that other studies are conducted to clarify this issue. Table 6 compares the results of studies analysing BP trajectories and CVD and mortality. In most cases, persistent high BP or increasing BP was associated with an increased risk of CVD, and control of BP was not systematically associated with a decreased risk of CVD.

Implications for clinical practice

An important finding of this study is that approximately half of the hypertensive subjects fell into the 'always treated and uncontrolled' group, which is consistent with other studies.[25 26] This highlights the need for healthcare providers to improve BP management and achieve better control among their patients. It is crucial for clinicians to recognise that simply prescribing antihypertensive medications might not be sufficient.[2 25] Ensuring that patients adhere to their treatment regimens and regularly monitoring and adjusting their BP levels are vital steps in optimising long-term cardiovascular health.

Strengths and limitations

This is one of the few population-based studies assessing the effect of BP status and BP trajectories on CVD events, CVD-related and all-cause mortality. Its long follow-up time allowed a reasonable number of events to occur and thus to assess the BP trajectories for a significant number of participants. Additionally, CVDs were meticulously collected and adjudicated and were not based on sole medical diagnosis or the international classification of diseases.

Several limitations should also be considered when interpreting the results. First, BP status and trajectories were based on single assessments, which could lead to misclassification of participants' BP status. This could partly explain the lack of association between untreated participants and cardiovascular events. Indeed, untreated subjects might have been falsely diagnosed as hypertensive and presented lower levels of obesity, diabetes and hypolipidemic treatment. Further studies should rely on a more precise evaluation of BP such as ambulatory BP monitoring. Second, it was not possible to account for treatment discontinuation before or during the study assessments, as it has been shown that approximately 22% of patients temporarily discontinue their antihypertensive treatment.[18] Third, our study was limited to an urban, mainly Caucasian population living in a high-income country, and it would be of interest if our results also apply to other settings. Fourth, one-fifth of the sample was excluded, which could have biased the results. Still, the results were similar after inverse probability weighting to account for exclusion. Finally, it was not possible to consider other potential confounding factors such as diet or physical activity. Hence, the issue of residual confounding cannot be ruled out.

Conclusion

In this population-based prospective study, participants with untreated or uncontrolled BP levels had a higher risk of CVD events and mortality (for untreated) than participants with normal BP levels. No significant benefit of BP control was found regarding CVD events, CVD-related or total mortality. BP trajectories were unrelated to CVD events, CVD-related or total mortality.

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Data availability statement Data are available upon reasonable request. The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

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