NON-PHARMACOLOGICAL DETERMINANTS OF HYPERTENSION AT THE POPULATION LEVEL

THESIS

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Abstract

BACKGROUND: Hypertension is the most common chronic disease worldwide and a significant risk factor for cardiovascular diseases. Modifiable risk factors contribute partially to an increasing prevalence and inadequate blood pressure control. On this basis, non-pharmacological recommendations are available in worldwide guidelines for the prevention and management of hypertension. These measures include: maintain a normal body weight, engage in regular physical activity, limit alcohol consumption, reduce dietary salt intake and adhere to a healthy diet.

OBJECTIVES: The objective of this thesis is to study the determinants of high blood pressure and to evaluate the relationship between lifestyle behavior and hypertension. In particular, the aim is to investigate the influence of an unhealthy behavior on blood pressure and the magnitude of the individual and combined effect of lifestyle factors on hypertension and blood pressure control.

METHODS: Cross-sectional analyses were conducted using data from a representative sample of the adult Lebanese population and the French CONSTANCES cohort study. The Lebanese sample consisted of 2088 adults aged 20 years and above randomly selected following a sampling scheme across Lebanon. While CONSTANCES is an ongoing prospective cohort that included between February 2012 and January 2018 a total of 87,808 volunteer participants aged 18–69 randomly selected from the National Health Insurance Fund. In both studies, blood pressure measurements were done following standard operational procedures and lifestyle behaviors were assessed using self-reported validated questionnaires. Mostly, logistic regression models and general linear models were used to estimate the magnitude of the associations and to study adjusted mean blood pressure parameters, respectively. Adjusted odds ratios were presented along with 95% confidence interval. Statistical analyses were conducted using different statistical analysis software.

RESULTS: Results of this thesis describe a high prevalence of hypertension and poor blood pressure control among treated individuals in the Lebanese population. While in France, epidemiologic data are in accordance with results of recent studies. From the conducted

analyses, increased body mass index (obesity and overweight), heavy alcohol consumption and non-adherence to dietary recommendations were seen to be independently associated with hypertension and poor blood pressure control, and they influenced systolic blood pressure levels. Controversial results were seen with physical activity in both studies and across different study populations. In terms of the magnitude of the association, body mass index and adherence to dietary approaches to stop hypertension (DASH) diet seem to have the biggest impact on increasing the odds of hypertension and uncontrolled blood pressure. Moreover, a combination of unhealthy behavior increased the odds of hypertension by more than 1.5 times, which highlighted the detrimental effect of an overall poor lifestyle on the risk of hypertension. Furthermore our findings suggest that the extent to which these factors are associated with hypertension is different by gender.

CONCLUSION: Findings of this thesis provided needed epidemiologic data on hypertension in Lebanon and France. They emphasize that non-adherence to widely recommended lifestyle modifications has important impact on the risk of hypertension and influences BP control. From a population-based perspective, these findings promote that a global healthy lifestyle through improvement of modifiable behaviors could have major benefits in the prevention of hypertension.

KEYWORDS: Hypertension, epidemiology, lifestyle factors, body mass index, DASH-diet

Résumé

CONTEXTE: L'hypertension est la maladie chronique la plus fréquente dans le monde et un facteur de risque majeur des maladies cardiovasculaires. Les facteurs de risque modifiables contribuent en partie à l'augmentation de la prévalence et au mauvais contrôle tensionnel. Dans ce contexte, des mesures non médicamenteuses sont largement recommandées dans les textes de recommandations des sociétés savantes afin de prévenir l'hypertension et/ou d'améliorer le contrôle tensionnel des individus hypertendus. Ces mesures comprennent : le maintien d'un poids normal, la pratique d'une activité physique régulière, une consommation d'alcool limitée, la réduction de la consommation de sel et l'adhérence à une alimentation équilibrée

OBJECTIFS: L'objectif de cette thèse est d'étudier les déterminants comportementaux de l'hypertension artérielle. En particulier, l'objectif est d'étudier l'influence d'un mode de vie malsain sur la pression artérielle ainsi que l'ampleur de l'effet individuel et de l'effet combiné des facteurs comportementaux sur l'hypertension et le contrôle tensionnel.

MÉTHODES: Des analyses transversales ont été menées d'une part sur un échantillon de 2088 adultes âgés de 20 ans représentatif de la population Libanaise et d'une autre part sur une cohorte d'adultes Français participants à l'étude prospective CONSTANCES. Entre Février 2012 et Janvier 2018, CONSTANCES est constituée d'un échantillon de 87 808 participants volontaires âgés de 18 à 69 ans représentatif de la caisse nationale d'assurance maladie. Les mesures de la pression artérielle ont été effectuées selon des protocoles opératoires standardisés et les données des comportements liés au mode de vie ont été recueillies à l'aide d'auto-questionnaires. Des modèles de régression logistique et des modèles linéaires généraux ont été utilisés pour estimer l'ampleur des associations et pour étudier les moyennes des paramètres de pression artérielle, respectivement. Les odds ratio ajustés ont été présentés avec un intervalle de confiance de 95%. Les données ont été analysées à l'aide de différents logiciels (SPPS and SAS).

RESULTATS: Les résultats de cette thèse décrivent une prévalence élevée d'hypertension et du mauvais contrôle chez les hypertendus traités dans la population Libanaise. Les données épidémiologiques issues de CONSTANCES semblent similaires à celles d'autres études

Françaises récentes. D'après les analyses effectuées, un indice de masse corporelle élevé (obésité et surcharge pondérale), une forte consommation d'alcool et la non adhérence aux recommandations nutritionnelles ont été significativement associés à l'hypertension et au mauvais contrôle tensionnel. De plus, ces facteurs sont associés à une augmentation du niveau de la pression artérielle systolique. Des résultats divergents ont été observés concernant l'activité physique et ceci dans les deux études et parmi les différentes populations étudiées. En termes d'ampleur de l'association, l'indice de masse corporelle et l'adhésion au régime DASH semblent avoir l'impact le plus important sur l'augmentation du risque d'hypertension et du contrôle tensionnel. De plus, une combinaison de comportements malsains multiplie par plus de 1,5 le risque d'hypertension, ce qui met en évidence les effets néfastes d'un mode de vie généralement malsain sur le risque d'hypertension. De plus, nos résultats suggèrent que l'ampleur de l'association de ces facteurs à l'hypertension diffère selon le sexe.

CONCLUSION: Les résultats de cette thèse rapportent des données épidémiologiques nécessaires sur l'hypertension au Liban et en France. Egalement, ces résultats suggèrent que la non-adhérence à l'ensemble des mesures non-médicamenteuses recommandées a un impact important sur le risque d'hypertension et influence le contrôle tensionnel.

MOTS-CLÉS: Hypertension, épidémiologie, facteurs comportementaux, indice de masse corporelle, alimentation

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List of Abbreviations

ACC: American College of Cardiology

ACE: Angiotensin Converting Enzyme

AHA: American Heart Association

ARB: Angiotensin II Receptor Blocker

ASCVD: Atherosclerotic Cardiovascular Disease

ATC: Anatomical Therapeutic Chemical

ATP: Adenosine Triphosphate

AUDIT: Alcohol Use Disorders Identification Test

BDS-22: Beirut Distress Scale

BMI: Body Mass Index

BP: blood pressure

CCB: Calcium Channel Blockers

CES-D: Center of Epidemiologic Studies Depression scale

CHD: Coronary Heart Disease

CI: Confidence Interval

CKD: Chronic Kidney Disease

CNAMTS: Caisse Nationale d'Assurance Maladie des Travailleurs Salaries

CNAV: National Retirement Insurance Fund (Caisse Nationale d'Assurance Vieillesse)

CO: Cardiac Output

CV: Cardiovascular

CVA: Cerebrovascular Accident

CVD: Cardiovascular Diseases

DASH: Dietary Approaches to Stop Hypertension

DBP: Diastolic Blood Pressure

DNA: Deoxyribonucleic Acid

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

ENNS: National Health and Nutrition Study (Étude Nationale Nutrition Santé)

ESC: European Society of Cardiology

ESH: European Society of Hypertension

FAs: Fatty Acids

FFQ: Food Frequency Questionnaire

HDL: High Density Lipoproteins

HEART: Hypertension Associated Risk Factors and Implications-project

HR: Hazard Ratio

HSCs: Health Screening Centers

HTN: Hypertension

INSERM: Institut National de la Santé et la Recherche Médicale

ISCED: International Standard Classification of Education

JNC 8: Joint National Committee

LBP: Lebanese Pound

LDL: Low-Density Lipoprotein

LMDS: Lebanese Mediterranean Diet Score

MAP: Mean arterial pressure

MD: Mediterranean Diet

MET: Metabolic Energy Turnover

MI: Myocardial Infarction

mPNNS-GS: modified National Program on Nutrition and Health – Guideline Score

MUFAs: Monounsaturated Fatty Acid

NHANES: National Health and Nutrition Examination Survey

NO: Nitric oxide

ORa: Adjusted Odds Ratio

PA: Physical Activity

PNNS: National Health and Nutrition Program (Progamme National Nutrition Santé)

PP: Pulse Pressure

PUFA: Polyunsaturated Fatty Acids

RAAS: Renin–Angiotensin–Aldosterone System

RCBG: Random Capillary Blood Glucose

RCT: Randomized Controlled Trials

RR: Relative Risk

SAS: Statistical Analysis System

SBP: Systolic Blood Pressure

SCORE: Systematic COronary Risk Evaluation

SES: Socioeconomic Status

SF-12: Short form-12

SFAs: Saturated Fatty Acid

SNIIRAM: National healthcare system claims database (Système National d'Informations Inter Régimes de l'Assurance Maladie)

SOP: Standard Operating Procedures

SPSS: Statistical Package for Social Sciences

TPR: Total Peripheral Resistance

USA: United States of America

WHO: World Health Organization

Publications and Thesis Diffusion

Original articles

Articles directly related to the objectives of the thesis

Cherfan M, Blacher J, Asmar R, Chahine M, Zeidan R, Farah R, Salameh P. Prevalence and risk factors of hypertension: A nationwide cross-sectional study in Lebanon. *J Clin Hypertens.* 2018; 20: 867–879. https://doi.org/10.1111/jch.13268

Cherfan M, Vallée A, Kab S, Salameh P, Goldberg M, Zins M, Blacher J. Unhealthy behavior and risk of hypertension the CONSTANCES population-based cohort. *Journal of Hypertension.* 2019; 37(11): 2180-2189 doi: 10.1097/HJH.0000000000002157

Cherfan M, Vallée A, Kab S, Salameh P, Goldberg M, Zins M, Blacher J. Unhealthy behaviors and risk of uncontrolled hypertension among treated individuals-The CONSTANCES population-based study. Submitted to *Scientific Reports* and being **reviewed after initial decision of major revision**

Michelle Cherfan, Alexandre Vallée, Sofiane Kab, Pascale Salameh, Marcel Goldberg, Marie Zins, Jacques Blacher. Predictors of uncontrolled blood pressure in hypertensive treated individuals – The CONSTANCES population based study. **Submitted for publication**

Articles indirectly related to the objectives of the thesis

Alexandre Vallée, **Michelle Cherfan**, Sofiane Kab, Valérie Olié, Marcel Goldberg, Marie Zins, Jacques Blacher. Determinants of hypertension: a decision tree model application in the CONSTANCES cohort. **Submitted for publication**

Goël Fenech, Alexandre Vallée, **Michelle Cherfan**, Sofiane Kab, Marcel Goldberg, Marie Zins, Jacques Blacher. Poor awareness of hypertension in France - The CONSTANCES population based study. **Submitted for publication**

Oral presentations

Cherfan M, Vallee A, Kab S, Salameh P, Goldberg M, Zins M, Blacher J. Determinants of poor blood pressure control among hypertensive treated individuals– The population- based CONSTANCES study. **39emes Journées de l'Hypertension Artérielle - 13th International Meeting of the French Society of Hypertension**, Paris, France, Decembre 19-20, 2019.

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Cherfan M, Blacher J, Asmar R, Chahine M, Zeidan RK, Farah R, Salameh P. Nonpharmacological determinants of hypertension: a nationwide cross-sectional study in Lebanon. **78th International pharmaceutical federation (FIP) world congress of pharmacy and pharmaceutical sciences.** Glasgow, United Kingdom, September 2-6, 2018

Poster presentations

Cherfan M, Vallee A, Kab S, Zins M, Blacher J. Unhealthy behavior and risk of uncontrolled hypertension among treated individuals – the constances cohort study. 38es Journées de l'Hypertension Artérielle - 12th International Meeting of the French Society of Hypertension, Paris, France, Decembre 13-14, 2018.

Cherfan M, Vallee A, Kab S, Zins M, Blacher J. Predictors of uncontrolled blood Pressure in hypertensive treated individuals – the constances cohort study. 38es Journées de l'Hypertension Artérielle - 12th International Meeting of the French Society of Hypertension, Paris, France, Decembre 13-14, 2018.

Cherfan M, Blacher J, Asmar R, Chahine M, Zeidan RK, Farah R, Salameh P. Prevalence and determinants of hypertension in the adult Lebanese population. 37es Journées de l'Hypertension Artérielle - 11th International Meeting of the French Society of Hypertension, Paris, France, Decembre 14-15, 2017.

CHAPTER 1: INTRODUCTION

Introduction

Hypertension (or high blood pressure) is the most common chronic disease and an important risk factor for cardiovascular diseases. It contributes to the burden of heart disease, stroke, kidney failure, dementia, premature death and disability. Over the years the prevalence of hypertension reached epidemic proportions, affecting over one quarter of the adult worldwide population; it is expected to further increase by 2025. Although the pathogenesis of primary hypertension is still not completely understood, the increasing prevalence is attributed to population growth, ageing and bio-behavioral risk factors. Lower socioeconomic status has also been associated with a poorer lifestyle risk profile such as diet and exercise and, in turn, with higher systolic blood pressure. Based on that, several lifestyle modifications or non-pharmacological approaches are widely recommended in worldwide guidelines for the management and prevention of hypertension. They are also adopted in the recommendations diffused by national public health agencies with efforts aimed at improving blood pressure level and delaying or preventing hypertension.

Nevertheless, from an epidemiological perspective, a quantification of the individual and combined effect of lifestyle factors on hypertension and uncontrolled blood pressure deserves further evaluation, especially from a population-based approach. In fact, in Lebanon, epidemiologic studies on hypertension are lacking, while in France, the presence of large prospective population-based studies "the French CONSTANCES cohort study" presents a major opportunity to provide further data on the determinants of hypertension and to study the effect of non-pharmacologic measures on blood pressure.

Therefore, the objective of this thesis is to study the risk factors associated with hypertension at the population level and to evaluate the relationship between lifestyle behavior and hypertension. Particularly, the aim is to investigate the influence of an unhealthy behavior on blood pressure and the magnitude of the individual and combined effect of lifestyle factors (alcohol, diet, physical activity, weight, psychological stress, and others…) on hypertension, using a large representative sample of the Lebanese population and in a cohort of French adults participating in the CONSTANCES study.

The thesis was conducted in a framework of an international joint supervision, between Universite Paris Nord-France and the Lebanese University-Lebanon. In France, research work is associated to the research unit "Centre of Research in Epidemiology and Statistics (CRESS)" to the research team "Equipe de Recherche en Epidemiologie Nutritionnelle (EREN)" (Institut National de la Santé et la Recherche Médicale-INSERM U1153) directed by Prof. Serge HERCEBERG. Also, research work was done in the research unit hosting the CONSTANCES database "Cohortes Epidemiologiques en population" (INSERM UMS011), directed by Prof. Marie ZINS. In addition, research and PhD related work was done at the office of Prof. Jacques BLACHER at Hotel Dieu hospital. In Lebanon research work was done in the research unit "Institut National de Santé Publique, Epidémiologie Clinique et Toxicologie" (INSPECT-LB), directed by Prof. Pascale SALAMEH.

The manuscript is divided into four parts, the first chapter presents a review of the literature on hypertension including epidemiologic data, pathophysiological mechanisms of arterial hypertension, and background information on modifiable risk factors describing the association between the different non-pharmacological approaches and blood pressure based on available data. Then, the objectives of the thesis are listed. The third chapter, details the methodology used; initially, the work done on the Lebanese sample will be described, then the methodology of CONSTANCES cohort study will be presented, followed by the methodological considerations used for the different analyses of this thesis. The last chapter, discusses the results of the work carried out, addresses methodological limitations and raises future research questions directly related to this work giving hypothesis opportunities for further research on this topic.

Review of the Literature

I. Hypertension

I.a Definition and Classification

Hypertension (HTN), also known as high blood pressure (BP), has been long identified as an important risk factor for cardiovascular diseases (CVD). It contributes to the burden of heart disease, stroke, kidney failure, dementia, premature death and disability **(World Health Organization. WHO/ DCO/WHD/2013.2)** and was found to be the number one risk factor in 2010 for Global Burden of Disease, as quantified by disability-adjusted life years **(Lim *et al.* 2013)**. Until recently, hypertension was defined as persistent elevation in arterial BP using cut-off values of systolic blood pressure (SBP) ≥140 mmHg and / or diastolic blood pressure (DBP) ≥90 mmHg. This was based on evidence from randomized controlled trials (RCT) that in patients with these BP values treatment-induced BP reductions are beneficial. This definition was used internationally to simplify the diagnostic approach and to facilitate the decision about treatment. It was adopted particularly by the « *European Society of Hypertension* » and « *European Society of Cardiology* » (ESH/ESC) **(Mancia *et al.* 2013)**, « *Joint National Committee* » (JNC 8) **(James *et al.* 2014)**, « *American College of Cardiology* » (ACC) and « *American Heart Association* » (AHA) **(Go *et al.* 2014**), and by the « *French Society of Hypertension* » **(Blacher *et al.* 2014).**

However, new guidelines for the diagnosis and management of hypertension have been recently published in the United States by the ACC/AHA **(Whelton *et al.* 2018)** and in Europe by the ESH/ESC **(Williams *et al.* 2018)**, underlining a major difference in the definition and classification of hypertension. This discrepancy is accentuated by changes regarding treatment, and the extent to which intensive blood pressure (BP) control should be achieved. These differences can have an impact on treatment attitudes and outcome incidence in hypertensive patients.

The ESC/ESH Guidelines maintained traditional BP categories, with grade 1 hypertension starting at an office BP of 140/90 mmHg. Conversely, the ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High BP in adults lowered the threshold for hypertension to 130/80 as a result of new evidence from RCTs. The European guidelines define a BP<120/80 as “optimal”, SBP between 120-129 and/or DBP 80-84 mmHg as “normal”, SBP between 130-139 and/or DBP between 85-89 mmHg as “high

normal" and SBP between 140-159 and/or DBP of 90-99 mmHg as "stage 1 hypertension" **(Williams *et al.* 2018)**. While in the new ACC/AHA guidelines, the definition of normal BP did not change from the previous document and remain as BP <120/80 mmHg, but it eliminated the classification of prehypertension and sub-divide the BP levels previously labelled "prehypertension" into "elevated BP" (SBP between 120 and 129 and DBP <80 mmHg), and "stage 1 hypertension" (SBP 130–139 or a DBP of 80–89 mmHg). For the diagnosis and classification of hypertension, both guidelines recommend that BP be measure in a healthcare setting (office pressures) and based on an average of ≥2 careful readings obtained on ≥2 occasions. **Table 1** presents the BP classification in both guidelines.

Extreme blood pressure elevations typically ≥180 and or ≥110 mmHg are referred to as stage 3 by the ESC/ESH Guidelines and in general, are commonly referred to as hypertensive crises. They are categorized as either hypertensive emergency or hypertensive urgency. Hypertensive emergencies are extreme BP elevations that are accompanied by acute or progressing end-organ damage. Hypertensive urgencies are extreme BP elevations without acute or progressing end-organ injury.

Patients are considered to have isolated systolic hypertension when their SBP values are elevated and DBP values are not, i.e. ≥130 mm Hg and <80 mm Hg in the case of the 2017 ACC/AHA guidelines and ≥140 mm Hg and <90 mm Hg for the European guidelines.

Table 1. Classification of office blood pressure and definitions of hypertension in adults according to Williams *et al.* 2018 and Whelton *et al.* 2018

	2017 ACC/AHA			2018 ESC/ESH		
Category	**SBP mmHg**		**DBP mmHg**	**SBP mmHg**		**DBP mmHg**
Optimal	---		---	<120	and	<80
Normal	<120	and	<80	120-129	and/or	80-84
High Normal	---		---	130-139	and/or	85-89
Elevated	120-129	and	<80	---		---
Hypertension stage / grade[a]						
1	130-139	or	80-89	140-159	and/or	90-99
2	≥ 140	or	≥ 90	160-179	and/or	100-109
3				≥ 180	and/or	≥ 110
ISH[b]				≥ 140	and	< 90

SBP = systolic blood pressure; DBP = diastolic blood pressure;
a 'Stage' for ACC/AHA; 'Grade' for ESC/ESH; ISH=Isolated systolic hypertension.
b Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated. Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
*BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions **(Whelton *et al.* 2018)**

I.b Epidemiology

Hypertension is the most common chronic disease with an estimated global prevalence of 1.13 billion individuals in 2015 **(NCD Risk Factor Collaboration, 2017)**. The overall prevalence of hypertension in adults is around 30-45%, with a global age standardized prevalence of 24 and 20% in men and women, respectively **(Chow *et al.* 2013)**. This high prevalence of hypertension is consistent across the world, irrespective of the country's income status. In Central and Eastern Europe the number of people with hypertension reached over 150 million individuals **(NCD Risk Factor Collaboration, 2017)**, in Arab countries, a recent review found that the overall estimated prevalence of HTN was of 29.5% **(Tailakh *et al.* 2014)**, in the US, the estimated prevalence is influenced by the choice of cutpoints to categorize hypertension; at the 140/90 threshold the prevalence of high blood pressure in adults ≥20 years is of 32% **(Chobanian *et al.* 2003, Whelton 2015)** while it is of 46% at the 130/80 level **(Whelton *et al.* 2018)**. Moreover, hypertension becomes progressively more common with advancing age, with a prevalence of >60% in people aged >60 years **(Chow *et al.* 2013, World Health Organization 2013)**. It is also expected that the worldwide prevalence of hypertension will continue to rise, increasing by 15-20% by 2025 and reaching close to 1.5 billion **(Kearney *et al.* 2005)**. This increase is attributed to population growth, aging and behavioral risk factors such as adopting a more sedentary lifestyle.

In addition to a high prevalence of hypertension, a number of epidemiological studies describe awareness, treatment and control rates among treated hypertensive individuals. It is commonly described as the 'rule of halves' for hypertension **(Hooker *et al.* 1999)** and states that: 'half the people with high blood pressure are not known (awareness), half of those known to be hypertensive are not treated (treatment) and half of those treated are not controlled (control). Comparative epidemiologic data between France, United States (US) and Lebanon is available in **Table 2**. In the US, data analysis from the National Health and Nutrition Examination Survey (NHANES) found that among treated individuals around 48% had uncontrolled BP at the 140/90 mmHg threshold **(National Center for Health Statistics US, 2014)**. Within Europe, BP control rate among hypertensive individuals reached 36% in England **(Falaschetti *et al.* 2014)**, 40% in Portugal **(Polonia *et al.* 2014)** and 51% in Germany **(Neuhauser *et al.* 2015)**. In France, two studies were conducted on a representative sample of the French population and results suggest no improvement in the prevalence and control of hypertension from 2006 until 2018. The National Health and

Nutrition study (Étude Nationale Nutrition Santé; ENNS) conducted in 2006-2007 **(Godet-Madirrossian *et al.* 2008)** described an estimated hypertension prevalence of 31% and poor BP control in 49.4% of hypertensive treated patients. While in 2015, the Esteban study reported rates of 30.6% and 50.4%, respectively **(Perrine *et al.* 2018),** it provides the following additional epidemiologic data **(Perrine *et al.* 2018):** Hypertension was more prevalent in men than in women (36.5% in men and 25.1% among women, p = 0.0001), it increased significantly with age, from 6.3% among 18-34 year olds to 67.8% among 65-74 year olds. Men had a higher prevalence of hypertension than women in all age classes. Regarding awareness, 55% of individuals with hypertension had knowledge of having hypertension. This proportion was more among women (62.9%) than among women men (50.1%). As for treatment, 70% of hypertensive individuals received treatment and there was no difference between sexes. Lastly regarding control among those treated, females had better BP control than men (60.1% vs. 41.4%). A breakdown of the prevalence, awareness, treatment and control of hypertension, between 2006 and 2015 if shown in **figure 1** and is stratified by gender. In Lebanon, limited epidemiologic studies were conducted. One study reported that the prevalence, awareness, treatment and control (among treated hypertensive) rates of HTN were 36.9%, 53%, 48.9%, and 54.2%, respectively **(Matar *et al.* 2015)**.

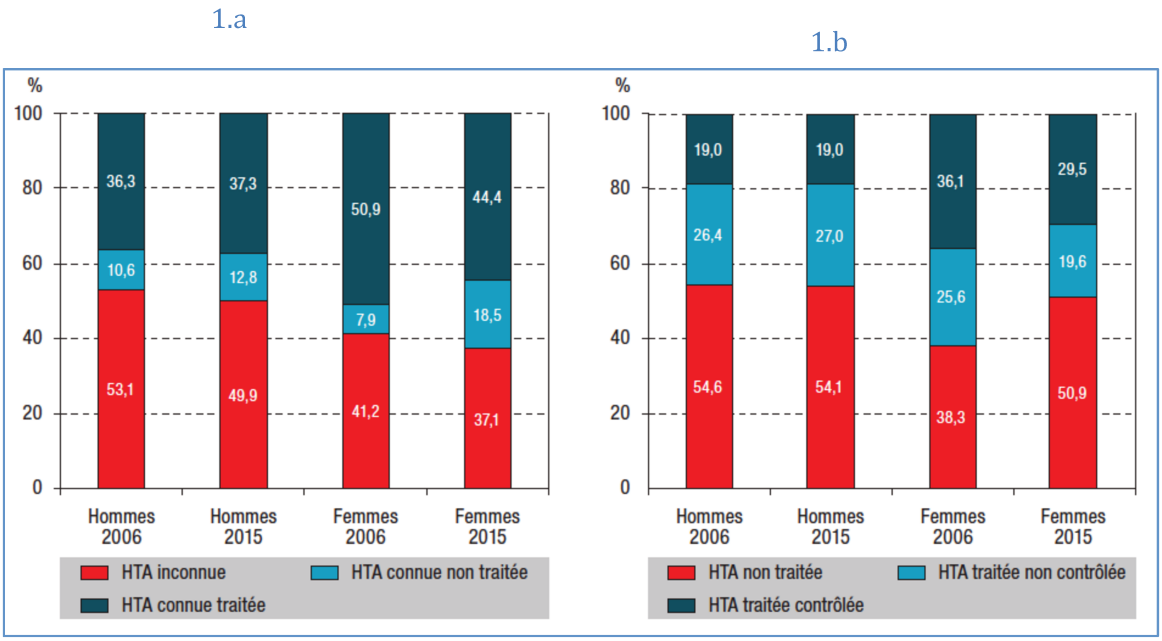


Figure 1. Evolution of Awareness (a), treatment and control of arterial hypertension (b) between ENNS 2006 and Esteban 2015, according to gender (Perrine et al. 2018).

Table 2. Comparative epidemiologic data on prevalence, awareness, treatment and control of hypertension in France, United States, and Lebanon (National Center for Health Statistics US 2014, Perrine *et al.* 2018, Matar *et al.* 2015)

	France Esteban study	United States NHANES 2012*	Lebanon
Total			
Prevalence of HTN	30.6%	32.5%	36.9%
Awareness	55.5%	---	53%
Treatment (in aware)	72.6%	---	93%
Treatment	47.3%	---	48.9%
Controlled (on treatment)	49.6%	47.4%	54.2%
Overall control	---	---	27%
Men			
Prevalence of HTN	36.5%	31.6%	42.7%
Awareness	50.1%	80.2%	50.4%
Treatment (in aware)	74.5%	88.4%	---
Treatment	45.9%	---	46.1%
Controlled (on treatment)	41.4%	69.5%	48.9%
Overall control	---	50.7%	---
Women			
Prevalence of HTN	25.1%	32.8%	29.5%
Awareness	62.9%	85.4%	57.9%
Treatment (in aware)	70.6%	94.4%	---
Treatment	49.1%	---	54%
Controlled (on treatment)	60.1%	68.5%	62.3%
Overall control	---	44.2%	---

HTN= Hypertension; NHANES = National Health and Nutrition Examination Survey
*Data based on hypertension definition using SBP/DBP ≥140/90 mm Hg according to JNC7
--- Data not available

I.c BP and CVD risk

Epidemiologic data demonstrate a strong correlation between BP and CV morbidity and mortality **(MacMahon *et al.* 1990)**. Risk of stroke, myocardial infarction (MI), angina, heart failure, kidney failure, or early death from a CV cause is directly correlated with BP. This relationship has been shown at all ages **(Vishram *et al.* 2012)** and in all ethnic groups **(Brown *et al.* 2007, Lawes *et al.* 2003)**, and extends from high BP levels to relatively low values. Data suggest that patients with elevated BP have an increased risk of CV disease **(Chobanian *et al.* 2003)**. In fact, a meta-analysis of 61 prospective studies showed that the risk of CVD increased in a log-linear fashion from SBP levels less than 115 mmHg and from DBP levels less than 75 mm Hg **(Lewington *et al.* 2002)**. Additionally, every 20/10 mm Hg increase in SBP and DBP respectively, was associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease.

Furthermore, population-based studies provided additional evidence about the association between BP and CV events. For example, a follow up study using data from 23,272 participants from the United States (US) National Health and Nutrition Examination Survey (NHANES) reported that more than 50% of deaths from coronary heart disease (CHD) and stroke occurred among those with hypertension **(Ford, 2011)**. Similarly, in the Atherosclerosis Risk in Communities study (ARIC), 25% of the CV events were attributable to hypertension **(Liao *et al.* 1996)**.

Additionally to hypertension being associated with CVD events, many patients with hypertension have other CVD risk factors, further influencing the development of CVD events. Common modifiable and relatively fixed risk factors for CVD among adults with hypertension are listed in **Table 3** and include cigarette smoking/tobacco smoke exposure, DM, dyslipidemia, overweight/ obesity, physical inactivity/low fitness level, and unhealthy diet **(Castelli, 1984)**. Observational studies have demonstrated that CVD risk factors frequently occur in combination **(Wilson *et al.* 1999)** and that the presence of multiple CVD risk factors in individuals with hypertension results in high absolute risks for CVD events **(Berry *et al.* 2012, Wilson *et al.* 1999)**. A meta-analysis from 18 cohort studies involving 257,384 patients found that adults with ≥2 CVD risk factors compared to those with only 1 risk factor had a substantially higher lifetime risk of CVD death, nonfatal MI, and fatal or nonfatal stroke. For this reason, recent guidelines and review articles highlighted the importance of using predicted CVD risk together with BP classification to guide antihypertensive drug therapy **(Muntner & Whelton 2017, Karmali & Lloyd-Jones 2017, Williams *et al.* 2018, Whelton *et al.* 2018)**. The European Guidelines have recommended use of the Systematic COronary Risk Evaluation (SCORE) system to estimate the 10-year risk of a first fatal atherosclerotic event (available at: http://www.escardio.org/ Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SC ORE-Risk-Charts). This scoring system is recommended for all hypertensive patients with no documented CVD, type 1 or type 2-diabetes, very high levels of individual risk factors or chronic kidney disease, to determine their need for treatment of their hypertension and other CV risk factors **(Williams *et al.* 2018)**. The 2017 ACC/AHA guidelines recommend using the use of the ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ ASCVD-Risk-Estimator/) that estimate 10-year risk of atherosclerotic CVD (ASCVD) event, to establish the BP threshold for treatment. Notably, the recommendations for stage 1 hypertension treatment are guided by the patients' underlying CV risk; use of BP-lowering medication is recommended for

primary prevention of CVD events for those with stage 1 hypertension and an estimated 10-year ASCVD risk of ≥ 10% **(Whelton *et al.* 2018)**.

Table 3. Common cardiovascular disease risk factors in adults with hypertension (Whelton *et al.* 2018)

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
Current cigarette smoking/ second hand smoking	Chronic kidney disease
	Family history
Diabetes mellitus	Increased age
Dyslipidemia/hypercholesterolemia	Low socioeconomic/educational status
Overweight/obesity	Male sex
Physical inactivity/low fitness	Obstructive sleep apnea
Unhealthy diet	Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.
†Factors that are difficult to change (chronic kidney disease, low socioeconomic/educational status, obstructive sleep apnea), cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce cardiovascular risk (psychosocial stress).

I.d Pathophysiology

The pathogenesis of essential hypertension is multifactorial and complex **(Gandhi *et al.* 2001)**. Multiple physiologic factors control BP and abnormalities of these factors are potential contributing components in the development of essential hypertension. These include malfunctions in either humoral (i.e, the renin–angiotensin–aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormones. As such, many interrelated factors may contribute to the increased blood pressure in hypertensive patients, and their roles may differ between individuals **(Beevers *et al.* 2001)**.

I.d.1 Blood pressure definitions and calculations

Arterial BP is the pressure in the arterial wall measured in millimeters of mercury (mm Hg). The two arterial BP values are *systolic BP* (SBP) and *diastolic BP* (DBP).

- SBP represents the peak value, which is achieved during cardiac contraction.
- DBP is achieved after contraction when the cardiac chambers are filling, and represents the nadir value.
- Pulse pressure (PP) is the absolute difference between SBP and DBP and is a measure of arterial wall tension.
- Mean arterial pressure (MAP) is the average pressure throughout the cardiac contraction cycle.
    - It can be used clinically to represent overall arterial BP, especially in hypertensive emergency.
    - During a cardiac cycle, two-thirds of the time is spent in diastole and one-third in systole. Therefore, the MAP is calculated by using the following equation: MAP = (SBP x 1/3) + (DBP x 2/3)
- Arterial BP is hemodynamically generated by the interplay between blood flow and the resistance to blood flow.
    - It is mathematically defined as the product of cardiac output (CO) and total peripheral resistance (TPR) according to the following equation:

BP = CO x TPR

        - CO is the major determinant of SBP, while TPR largely determines DBP.
        - In turn, CO is a function of stroke volume, heart rate, and venous capacitance.

I.d.2 Cardiac output and peripheral resistance

For normal blood pressure, a balance between the cardiac output and peripheral vascular resistance is needed (**Figure 2**). Most of hypertensive patients have a normal cardiac output, however the peripheral resistance is increased. The small arterioles which walls contain smooth muscle cells determine the peripheral resistance. The contraction of smooth muscle cells has been associated to an increase in intracellular calcium concentration, thus the vasodilatory effect of drugs blocks the calcium channels **(Beevers *et al.* 2001)**. It is possible that prolonged smooth cells contraction induces structural changes in thickening of the arteriolar walls, mediated by angiotensin, resulting into a permanent rise in peripheral resistant **(Beevers *et al.* 2001)**. In early hypertension, it has been postulated, that the peripheral resistance is not raised while the increment of the blood pressure is due to an increase of the cardiac output, related to sympathetic overactivity. Then a compensatory mechanism raises the peripheral arteriolar resistance to prevent the raised pressure, which would affect cell homeostasis **(Hall 2001)**.

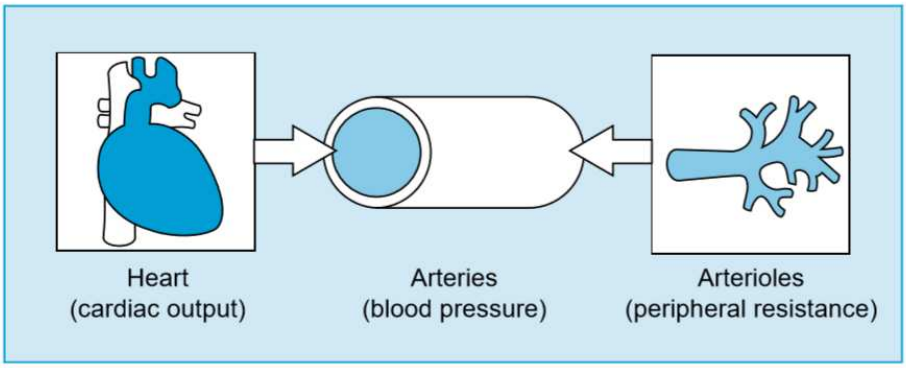


Figure 2. The heart, arteries and arterioles in hypertension (Beevers et al. 2001)

I.d.3 Renin-angiotensin system

The renin-angiotensin system could be the most important system involved to control blood pressure (**Figure 3**). The kidney secretes an enzyme, renin, as a consequence of underperfusion, reduction of salt consumption or in response to stimulation from the sympathetic nervous system **(Beevers *et al.* 2001)**. This enzyme is responsible for converting angiotensinogen to angiotensin I, an inactive substance that is in turn rapidly converted by angiotensin converting enzyme (ACE) to angiotensin II. Angiotensin II is a potent vasoconstrictor provoking the increase of blood pressure. Also, it stimulates the release of aldosterone (a hormone that inhibits the excretion of sodium in the urine) that increases blood pressure due to sodium and water retention **(Hall 2001)**. The

interrelationship between the kidney, angiotensin II and regulation of blood pressure is illustrated in **Figure 3** and is briefly described below.

Circulating angiotensin II can elevate BP through pressor and volume effects. Pressor effects include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and centrally mediated increases in sympathetic nervous system activity. Angiotensin II also stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption that increases plasma volume, TPR, and ultimately BP. Aldosterone also has a deleterious role in the pathophysiology of other CV diseases (eg, heart failure, myocardial infarction (MI), kidney disease) by promoting tissue remodeling leading to myocardial fibrosis and vascular dysfunction **(Bastard *et al.* 2013)**. Clearly, any disturbance in the body that leads to activation of the RAAS could explain chronic hypertension **(Zhang & Harris 2015)**.

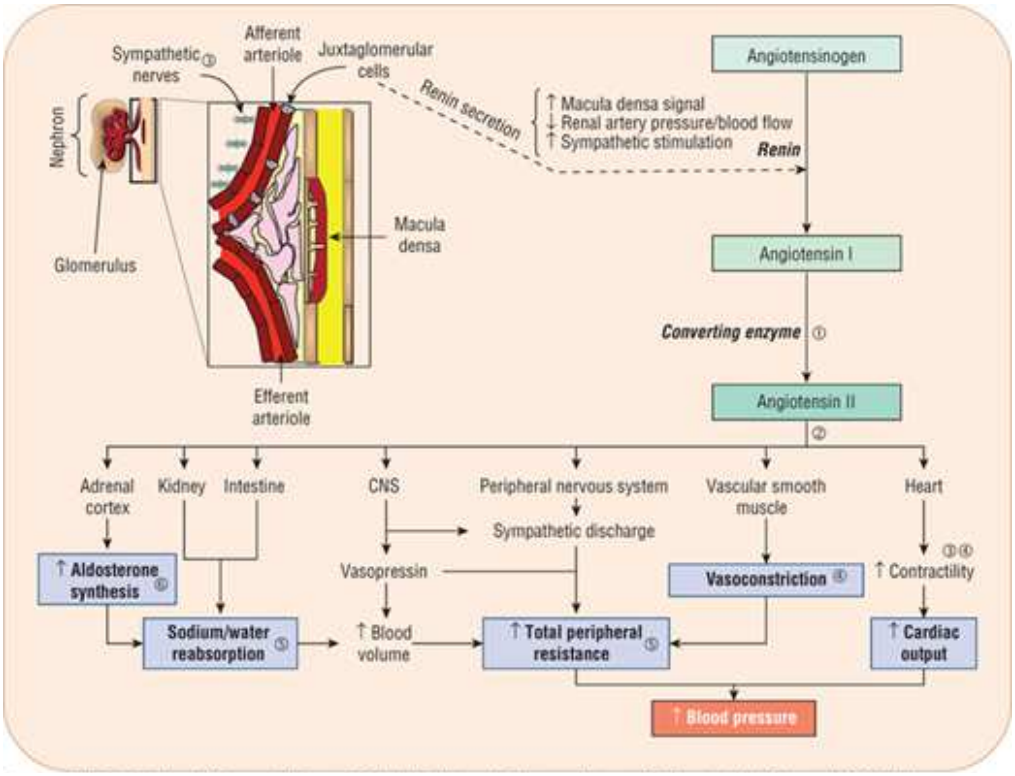


Figure 3. Diagram representing the renin-angiotensin-aldosterone system (Dipiro *et al.* 10th edition).

The primary sites of action for major antihypertensive agents are included:
1. ACE inhibitor; 2. Angiotensin II receptor blocker (ARB); 3. Beta-blockers; 4. Calcium channel blocker; 5. Thiazide; 6. Mineralocorticoid receptor antagonist

I.d.4 Autonomic nervous system

Arteriolar constriction and arteriolar dilatation can be provoked by the stimulation of the sympathetic nervous system. Therefore, this system has an important role for maintaining a normal blood pressure, particularly in short term control of blood pressure (stress or physical activity). Noradrenaline is a powerful vasoconstrictor hormone, as well as adrenaline but this last has less power **(Hall 2001)**. Little evidence suggested a clear role of epinephrine (adrenaline) and norepinephrine (noradrenaline) in the etiology of hypertension **(Beevers *et al.* 2001)**. However, drugs that block the sympathetic nervous system have a well-established role by lowering blood pressure. Probably, hypertension is mediated by interactions between the autonomic nervous system, the renin-angiotensin system, together with other factors, like sodium, circulating volume, and some hormones **(Beevers *et al.* 2001)**.

I.d.5 Endothelial dysfunction

The cells in the vascular endothelial produce a number of potent vasoactive agents playing a key role in cardiovascular regulation. The endothelium produces nitric oxide (NO) a vasodilator molecule and endothelin a vasoconstrictor peptide being the major regulators of blood pressure and vascular tone **(Beevers *et al.* 2001)**. In hypertensive patients the balance between vasodilator and vasoconstrictor molecules is upset, leading to changes in the endothelium and their functions. The antihypertensive therapy seems to restore the impaired on the production of NO, but not to repair the damaged endothelium dependent vascular relaxation to endothelial agonist. This could indicate that such endothelial dysfunction is primary and irreversible once hypertensive process is established **(Beevers *et al.* 2001)**.

I.d.6 Vasoactive substances

There are other vasoactive systems and mechanisms that affect sodium transport and vascular tone that are involved into the control of blood pressure. Nonetheless, their contribution is unclear in the development of hypertension **(Beevers *et al.* 2001)**. For example, bradykinin is a peptide with vasodilators properties, which can be inactivated by angiotensin converting enzyme. Probably, ACE inhibitors may affect BP by also blocking bradykinin inactivation. Another molecule is endothelin, a powerful endothelial vasoconstrictor, which may produce a salt sensitive increase on blood pressure and also can

activate local renin angiotensin systems. Also, the secretion of the atrial natriuretic peptide hormone by the heart induces a raise of blood volume. This hormone increases sodium and water excretion from the kidney similar as a natural diuretic, fluid retention and hypertension may be caused by a failure of this system **(Beevers *et al.* 2001)**.

I.d.7 Sodium and potassium

The excess intake of sodium, especially in the form of sodium chloride, and the reduced consumption of potassium intake, are determinants along with other factors, of an increase in the incidence of hypertension **(Beevers *et al.* 2001)**. Sodium is the main extracellular cation and has been considered the most important dietary factor affecting BP and developing hypertension. In contrast, potassium is the main intracellular cation usually viewed as a minor factor in hypertension, although the evidence showed that the deficiency of this nutrient has a critical role **(He & MacGregor 2001)**.

There is a relation between sodium and potassium intake, through the Na/K ATPase enzyme. This solute pump allows potassium ions into the cells and pumps sodium ions out against their concentration gradients. This is an active pumping using energy from the ATP molecule (Adenosine triphosphate), thus for each ATP molecule used, two ions of extracellular potassium and three ions of intracellular sodium are exchanged **(Forrest 2014)**. The excess of sodium intake is absorbed in the intestine, provoking an increase in plasma osmolality. This stimulates the sensation of thirst and forces the consumption of water with the consequent expansion of the intravascular volume. To compensate and control this increase in volume, the kidneys respond by eliminating the overload of sodium and water **(Borst & Borst-De Geus 1963)**. On the other hand, a decrease of potassium intake causes a deficit of potassium in the cells which in order to maintain their tonicity and tone volume gain sodium **(Adrogue & Madias 2007)**.

The modern western diet is rich in sodium and poor in potassium intake, and kidneys are not adapted to this new dietary pattern. On the contrary, prehistoric diets were rich in potassium and poor in sodium thus the kidneys were poised to conserve sodium and to eliminate potassium. This new diet interacts with the kidneys, resulting in an excess of sodium and a deficit of potassium in the body, which increases peripheral resistance leading to hypertension (**Figure 4**) **(Adrogue & Madias 2007)**.

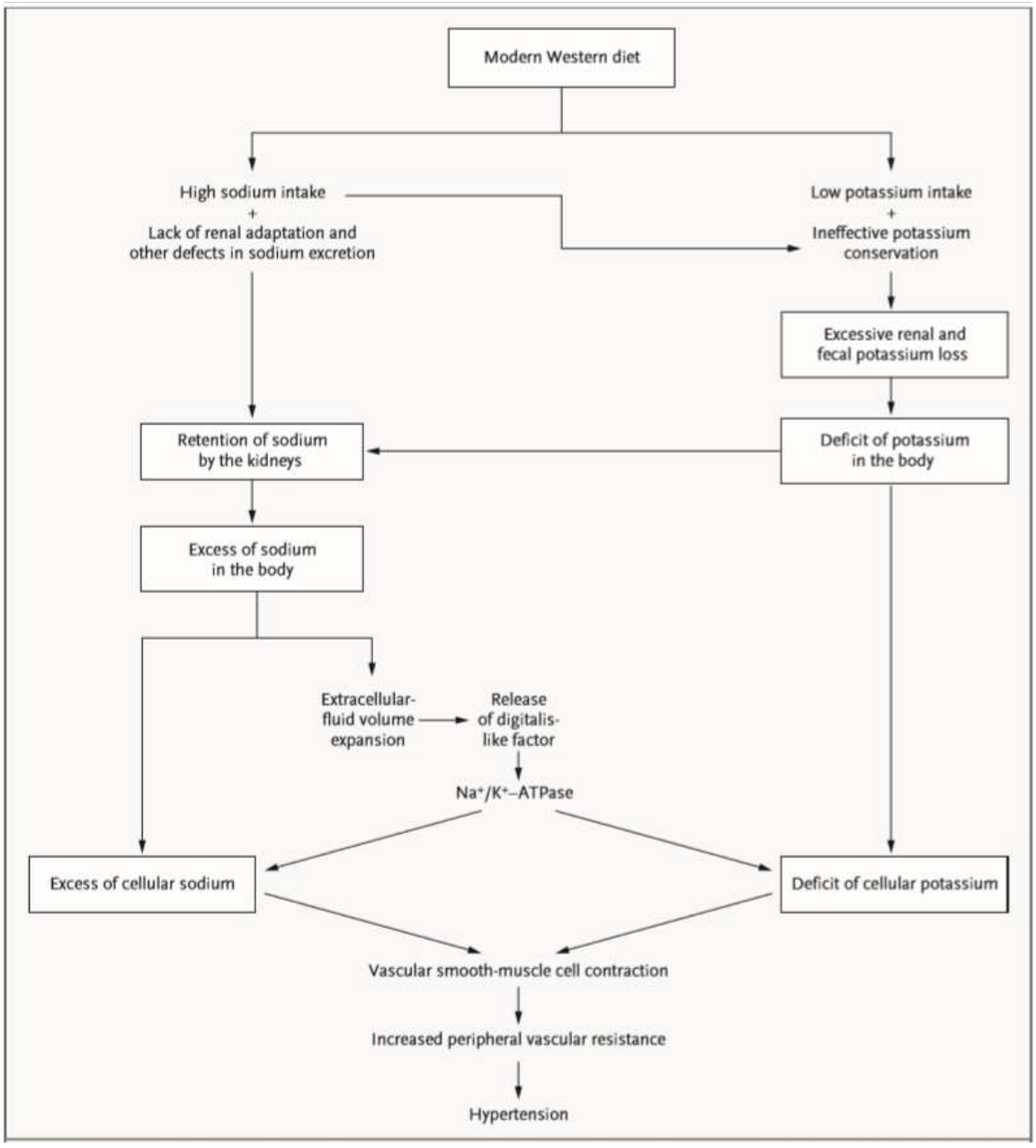


Figure 4. Interaction of the modern western diet and kidneys in the pathogenesis of hypertension (Adrogue &Madias, 2007).

I.d.8 Control of Blood pressure

Blood pressure increase due to cardiac output can occur in two ways. The first is a direct route, due to the increase in blood volume. This situation triggers a series of processes (increased circulatory filling, venous blood heart return), which increase cardiac output and therefore blood pressure (**Figure 5**). The second way is indirect, through self-regulation. As its name indicates, this is when the tissue that regulates the blood flow, due to an excess of blood flow, causes the vessels to constrict and reduce the passage of blood to normalize it. This mechanism increases the total peripheral resistance and thus increases the blood pressure (**Figure 5**) **(Hall 2001)**.

Many systems contribute to maintain blood pressure homeostasis, such as for short-term control, the sympathetic nervous system, and for long term, the kidneys. Faced with a drop-in pressure, the sympathetic nervous system secretes noradrenaline. This substance works as a vasoconstrictor and acts at the artery and small arteriole level, in this way it increases the peripheral resistance and consequently the arterial pressure **(Couch & Krummel 2009)**.

The kidneys regulate blood pressure by controlling the extracellular fluid **(Couch & Krummel 2009)**. In cases of excess extracellular fluid, the blood volume, and consequently, the blood pressure rises. This pressure elevation has a direct action on the kidneys, which excrete the exceeding extracellular fluid in order to normalize the blood pressure. The kidneys, in addition to regulating the pressure through the extracellular fluid, also have the renin-angiotensin system for this purpose **(Hall 2001)**.

Angiotensin II has two main effects at the circulatory level. Firstly, it causes vasoconstriction in the arterioles (and to a lesser degree, in the veins). The arteriole constriction increases the peripheral resistance, which in turn raises the blood pressure. Secondly, it increases blood pressure by decreasing the renal excretion of sodium and water. In this way, the volume of extracellular fluid increases progressively and consequently, the blood pressure, which is a slightly longer process, taking between hours and days **(Hall 2001)**.

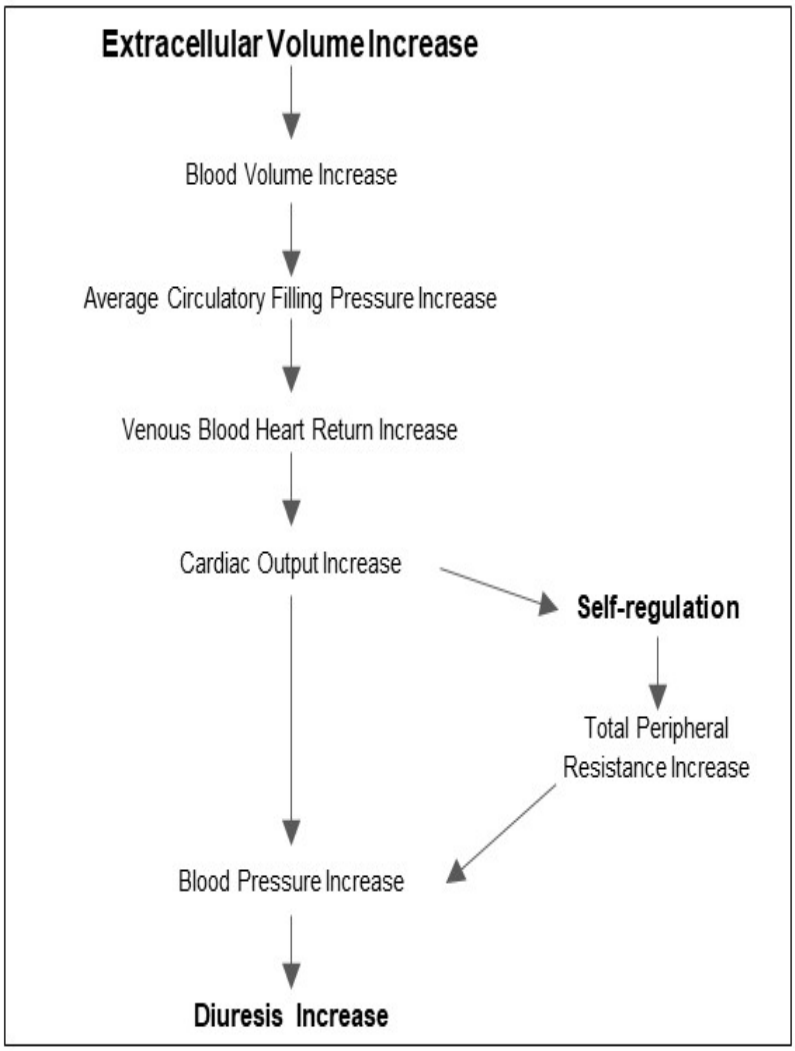


Figure 5. Mechanisms by which the increase in extracellular volume raises blood pressure (Hall, Treaty of Medical Physiology, 10th edition).

I.e Etiology

Hypertension can be divided into primary or secondary forms. Primary (essential) hypertension accounts for the vast majority (≥90%) of cases while secondary hypertension is seen in approximately 10% of adults and is when a remediable cause of hypertension can be identified. If the cause can be accurately diagnosed and treated, patients with secondary hypertension can achieve normalization of BP or marked improvement in BP control, with concomitant reduction in CVD risk **(Whelton *et al.* 2018)**.

The common and uncommon causes of secondary hypertension are listed in Table 4. The majority of patients with secondary hypertension have primary aldosteronism or renal

parenchymal or renal vascular disease, whereas the remainder may have more unusual endocrine disorders or drug- or alcohol-induced hypertension. In addition, numerous substances, including prescription medications, over-the-counter medications, herbals, and food substances, may affect BP (Table 4).

Table 4. Causes of secondary hypertension* (Whelton *et al.* 2018).

Disease Induced	Medications Induced
Common causes	Alcohol
Renal parenchymal disease	Amphetamines (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine)
Renovascular disease	
Primary aldosteronism	Antidepressants (eg, MAOIs, SNRIs, TCAs)
Obstructive sleep apnea	Atypical antipsychotics (eg, clozapine, olanzapine)
Drug or alcohol induced	Caffeine
Uncommon causes	Decongestants (eg, phenylephrine, pseudoephedrine)
Pheochromocytoma/para ganglioma	Herbal supplements (eg, Ma Huang [ephedra], St. John's wort [with MAO inhibitors, yohimbine])
Cushing's syndrome	
Hypothyroidism	Immunosuppressants (eg, cyclosporine)
Hyperthyroidism	Oral contraceptives
Aortic coarctation (undiagnosed or repaired)	NSAID
Primary hyperparathyroidism	Recreational drugs (eg, "bath salts" [MDPV], cocaine, methamphetamine, etc.)
Congenital adrenal hyperplasia	
Mineralocorticoid excess syndromes other than primary aldosteronism	Angiogenesis inhibitor (eg, bevacizumab) and tyrosine kinase inhibitors (eg, sunitinib, sorafenib)
Acromegaly	Systemic corticosteroids

*List is not all inclusive. MAOI, monoamine-oxidase inhibitors; MDPV, methylenedioxypyrovalerone; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitor; and TCA, tricyclic antidepressant

Primary hypertension originates from a combination of genetic and environmental factors. Although the genetic predisposition to hypertension is nonmodifiable and conveys lifelong CVD risk, the risk for hypertension is modifiable and largely preventable due to a strong influence by key environmental/lifestyle factors. The most important of these factors, which often are gradually introduced in childhood and early adult life, are weight gain leading to overweight/obesity, unhealthy diet, excessive dietary sodium and inadequate potassium intake, insufficient physical activity, and consumption of alcohol **(Whelton *et al.* 2018)**. Although hypertension is a consequence of a combination of environmental and genetic risk factors, social determinants of health are also risk factors for hypertension. **Figure 6** depicts the major pathophysiological determinants of BP in primary hypertension, which are further elaborated below.

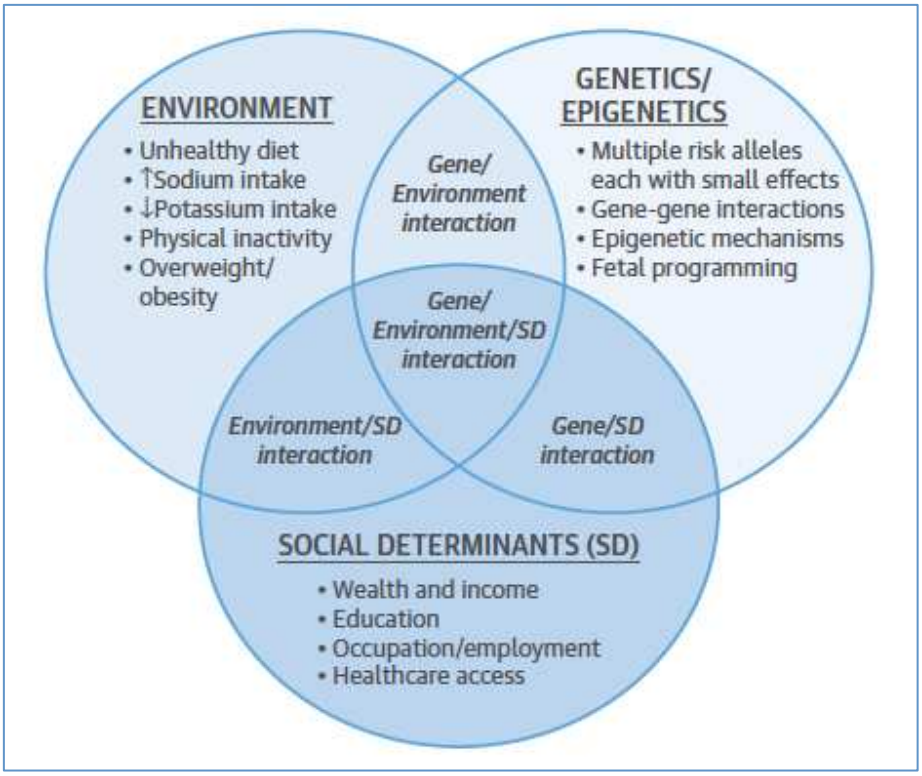


Figure 6. Major determinants of blood pressure in primary hypertension and their interaction in adults (Carey et al. 2018).

SD= social determinants; ↑increased; ↓decreased

Genetic/epigenetic, environmental, and social determinants interact to increase BP in virtually all hypertensive individuals and populations.

II. Non-Modifiable risk factors and hypertension

II.a Age and Genetics

Hypertension can originate from the alteration of a single gene or a set of them. However, most cases of hypertension are of polygenetic origin in which many genes and/or combination of genes influence BP **(Padmanabhan *et al.* 2015, Dominiczak & Kuo 2017)**, that is, two individuals may suffer from hypertension without having the same affected genes. Common genetic variants influencing BP have been identified at over 300 independent genetic loci, but In general, the altered genes are directly or indirectly related to the renal reabsorption of sodium and to the expression of the angiotensin renin system **(Maicas *et al.* 2003)**. Approximately 30% of the variability of blood pressure is attributed to genetic factors **(Corvol *et al.* 1992)** but the associated variants have overall only small effects on BP; in fact studies show that the collective effect of all BP loci identified through genome-wide association studies accounts for only about 3.5% of BP variability **(Ehret *et al.* 2016, Surendran *et al.* 2016)**. Several studies have found an association of blood pressure between siblings and between parents and children **(Barlassina *et al.* 2002)**. In addition, to specific genes there is evidence that family history hypertension increases its risk. Thus, the increase in the risk of hypertension has been consistently observed in those subjects who had a family history, due to hereditary factors, but also due to learning of lifestyle factors specific to the family **(De Cruz Benayas *et al.* 2008)**. National screening programs have found that the prevalence of hypertension is twice in those who have a family history of hypertension compared to those who did not **(De Cruz Benayas *et al.* 2008)**.

Age is a major risk factor for high blood pressure, as changes in the vascular system occur over time. The arteries harden as they lose elasticity, oxidative stress increases and, in general, the activity of the antioxidant system decreases **(Rybka *et al.* 2011)**, thus favoring a blood pressure increase. In women, the prevalence of hypertension increases near 50 years of age and continues until their 80s **(Maicas *et al.* 2003)**, as seen earlier related to hypertension prevalence. The Framingham study showed that the risk of a cardiovascular event among American aged between 50 and 60 years old was 37% for men and only 6% for women, although after 65 years, the risk is higher for women **(Texas Heart Institute 2018)**. In the near future, with aging of the population, hypertension will be a disease more common in women than in men **(Hage *et al.* 2013)**.

II.b Socioeconomic status

Social determinants of health are broadly defined as "the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness" **(Havranek *et al.* 2015)**. Socioeconomic status (SES) signifies socially defined economic factors that influence the positions that individuals or groups hold within the stratified structure of a society. SES includes wealth and income, education, employment/occupation status, access to health care, and other factors. Although social determinants are most often invoked in discussions of inequalities or disparities, social factors affect cardiovascular health in virtually all people **(Havranek *et al.* 2015)**. A meta-analysis concluded that a low SES was associated with an increase of hypertension risk. This association was particularly important with the level of education; participants with lower education doubled their risk of presenting hypertension (Odds ratio (OR) 2.02; 95% confidence interval (CI) 1.55 - 2.63) **(Leng *et al.* 2015)**. Furthermore, in other reports, countries with lower income presented a greater number of habitants who were unaware of their disease (37.9% vs. 67.0%), treatment (29.0% vs. 55.6%) and hypertension's control (7.7% vs 28.4%) with respect to countries with higher income (**Mills *et al.* 2016)**. Probably, the difficulties to access to medical care, a weak health system, and less capacity to confront the burden of the disease may explain the differences observed. Thus, the conditions of living and working delay the diagnostic and treatment of hypertension, which can contribute to the prevention of its complications (**World Health Organization 2013)**.

III. Modifiable risk factors and hypertension

Various environmental exposures and lifestyle behaviors, including components of diet, eating habits, physical activity, obesity, smoking and alcohol consumption, influence BP.

III.a Dietary components

III.a.1 Dietary salt (sodium) intake

As described above, sodium plays an important role in the pathophysiology of hypertension. Sodium is actually found in salt, with 0.5g of salt providing 200mg of sodium and approximately 70% of the sodium intake results from addition during processing of foods, including breads, salted meats, canned goods, cereals, pastries, and food preparation (fast-food and sit-down restaurants) **(Food and Drug Administration, Center for Food Safety and Applied Nutrition 2016, Harnack *et al.* 2017)**. According to the world health organization (WHO) the current dietary salt intake in most countries around the world is of 9-12 g/day, further suggesting that daily Na+ intake of 2400 mg/24h (5-6 g of salt) to be considered as normal/beneficial **(World Health Organization 2006)**, but excessive sodium intake of more than 5000mg (12.5g of salt) to be an important determinant of hypertension and other CVD **(O'Donnell *et al.* 2015, Whelton *et al.* 2012)**. In fact in numerous cross-sectional, prospective cohort and experimental studies, sodium intake is positively correlated with BP and accounts substantially for the age-related rise in BP **(Elliott *et al.* 1996, Takase *et al.* 2015, Jackson *et al.* 2018)**. Conversely, sodium restriction has been shown to have a BP-lowering effect in many trials. Of these studies, the INTERSALT study was one of the first large international epidemiologic studies on sodium intake and hypertension and reported that lowering sodium intake by 100mmol was associated with a 3mmHg decrease in SBP **(Elliott *et al.* 1996)**. Similarly, the Dietary Approaches to Stop Hypertension (DASH)-Sodium study was conducted on patients with or without hypertension, to evaluate the effect of "Control Diet Group" (typical US diet) or "DASH Diet Group" on BP. Each diet group consumed high, intermediate, or low Na+ food (150, 100 and 50 mmol/day) for 30 consecutive days in random fashion. The results of this study revealed that reducing the Na+ intake from high to intermediate level resulted in SBP reduction of 2.1 mmHg in "Control Diet Group" and 1.3 mmHg in "DASH Diet Group". Similarly, the reduction from intermediate to low level Na+ intake resulted in further reduction of 4.6 mmHg in "Control Diet Group" and 1.7 mmHg reduction in "DASH Diet

Group" **(Sacks *et al.* 2001)**. In comparison to Control Diet with high Na+ intake, the DASH diet with low Na+ content led to SBP reduction of 11.5 mmHg in hypertensive individuals **(Sacks *et al.* 2001)**. A recent meta-analysis of these trials showed that a reduction of 1.75 g sodium per day (4.4 g salt/day) was associated with a mean 4.2/2.1 mmHg reduction in SBP/DBP, with a more pronounced effect (-5.4/ -2.8 mmHg) in people with hypertension **(He *et al.* 2013)**. Additionally, data from studies revealed that the BP-lowering effect of sodium restriction is greater in those whose BP is salt sensitive such as in black people, in older patients, in diabetes and chronic kidney disease (CKD) **(Weinberger *et al.* 1986, Suckling *et al.* 2016)**.

Furthermore, dietary sodium restriction has been reported to augment the BP-lowering effects of anti-hypertensive medications. Previous data suggest that among adults with hypertension being treated with BP lowering medications, sodium reduction further reduces SBP by about 3 mm Hg and may reduce the number or dose of BP-lowering drugs that are necessary to control BP **(Whelton *et al.* 1998)**. In this context, a reduction in sodium intake may also lower SBP significantly in individuals with resistant hypertension who are taking multiple antihypertensive medications **(Pimenta *et al.* 2009)**.

On the other hand, prospective studies reported that reducing sodium intake below a certain level (about 3 g of sodium per day) further reduced BP, but paradoxically was associated with an increased risk of all-cause and CV mortalities in both the general population and in hypertensive people, suggesting a J-curve phenomenon **(Mente *et al.* 2016)**. The mechanism of this apparent increased risk at low sodium intake is not well understood and might be confounded by reverse causality.

Nevertheless, in the presence of available data on sodium restriction and BP, public health bodies advocate a reduction in dietary salt consumption at the population level but future research may inform aspects of optimal sodium reduction strategies and the intake targets for populations.

III.a.2 Calcium and vitamin D

There are contradictory evidences on the role of Ca+2 in lowering BP. Mierlo et al. in a meta-analysis reported the BP lowering effect of Ca+2 supplementation **(Mierlo *et al.* 2006)**. On the contrary, a retrospective study reported that prevalence of hypertension was higher in patients with hypercalcemia **(Yagi *et al.* 2014)**. In the Women Health Study including 28 886 participants, dietary intake of calcium but not calcium from

supplementation, was associated with a decrease of hypertension risk **(Wang *et al.* 2008)**. A Cochrane review on 15,000 pregnant women revealed that high Ca+2 intake decreased the risk of hypertension during pregnancy **(Hofmeyr *et al.* 2010)**.

On the other hand, a few epidemiological studies suggest that vitamin D deficiency may lead to development of hypertension **(Wang *et al.* 2008, Forman *et al.* 2007)**. Several clinical studies have been carried out to examine the antihypertensive effect of vitamin D supplementation, but no consistent results were found. A 3-month randomized controlled trial involving 283 black participants revealed that for each 1 ng/ml increase in plasma 25, hydroxyvitamin D, there was 2.0 mmHg reduction in SBP; on the other hand, there was no effect on DBP **(Forman *et al.* 2013)**. These results were similar in a meta-analysis that found that vitamin D supplementation significantly decreased systolic but not DBP **(Wu *et al.* 2010)**. Another more recent meta-analysis reported SBP reductions of 1.96 mmHg (95% CI 0.36 to 3.57 mmHg) and DBP reductions (-0.09; 95% CI -0.21 to - 0.03 mmHg), but they were not significant when compared with the placebo **(Qi *et al.* 2017)**. In 2017, a meta-analysis of RCTs evaluated the effect of the supplementation of calcium plus vitamin D on blood pressure. The follow-up time ranged from 15 weeks to 7 years and included 36 806 participants. The study showed no significant effect on DBP reduction, and the pooled weighted mean differences was -0.22 mmHg (95% CI -0.89 to 0.46; p = 0.53) **(Zhen *et al.* 2017)**. However there was evidence of significant heterogeneity, which means there was variability in the studies considered in the meta-analysis due to differences in participants, interventions or outcomes, in the study design, risk of bias as well as variation in intervention effects or results **(Fletcher 2007)**.

Vitamin D is critically for calcium absorption and homeostasis, both nutrients are often administrated together. According to a number of studies in humans and animals, dietary calcium which main source is dairy products, forms insoluble calcium soaps with fatty acids (FAs) or bind of bile acids. In this way, calcium interferes with the absorption of fat in the intestine, resulting in the decrease of the digestible energy from diet through a higher excretion of fecal fat **(Christensen *et al.* 2009)**.

To date, the available data from the literature do not support the use of calcium and/or vitamin D or its analogues in the treatment of hypertension. Additional data is needed to further provide evidence and clarify this association.

III.a.3 Potassium and magnesium

- **Potassium**

The large international INTERSALT study, observed that potassium intake measured by 24-hour urinary potassium excretion was an important and independent determinant of blood pressure. An increase of potassium intake of 30-40 mmol was associated with a reduction of 2 - 3 mmHg in average **(Dyer *et al.* 1994)**. In this study, it is important to mention that the ratio between sodium and potassium had also a significant inverse association with blood pressure having a stronger statistical association than sodium and potassium individually. Moreover, in a meta-analysis of RCTs **(Whelton *et al.* 1997)**, potassium supplementation was associated with a decrease on blood pressure. In average they observed a significant reduction on SBP and DBP of -3.11 mmHg (95% CI -1.91 to -4.31 mmHg) and -1.97 mmHg (95% CI -0.52 to -3.42 mmHg), respectively. The effect was greater in participants exposed to a low consumption of sodium. Previous studies suggested that the balance between sodium and potassium intake seems to be more important than the individual intake of both of them. A probable explanation is a possible additive effect when potassium intake is increased and sodium intake is reduced **(He & MacGregor 2001)**.

A diet rich in potassium increase plasma potassium as well as provoke endothelium-dependent vasodilatation stimulating the sodium pump and opening potassium channels **(Haddy *et al.* 2006)**. Additionally, potassium can influence blood pressure by natriuresis, modulation of baroreceptor sensitivity, reduced vasoconstrictive sensitivity to norepinephrine and angiotensin II, increased serum and urinary kallikrein, increased sodium/potassium ATPase activity, alter the synthesis of DNA, and the proliferation in vascular smooth muscle and sympathetic nervous system cells **(Das 2001, Preuss 1997)**. Furthermore, the homeostasis of both sodium and potassium plays a critical role in endothelium-dependent vasodilatation **(Panza 1990)**. The synthesis of NO decreases due to sodium retention, which can also cause an arteriolar vasodilator elaborated by endothelial cells, and increases the plasma level of asymmetric dimethyl-L-arginine, an endogenous inhibitor of NO production **(Fujiwara *et al.* 2000, Houston & Harper 2008)**.

- **Magnesium**

Observational studies supported a role of magnesium intake in development of hypertension. A meta-analysis **(Han *et al.* 2017)** of nine cohorts' studies including 180 566 participants and 20 119 cases of hypertension found an inverse relation between dietary

magnesium and risk of hypertension. They reported 8% less risk of hypertension when they compared the participants in highest with lowest quintiles of consumption (RR 0.92; 95% CI 0.86 - 0.98). Also, a 5% reduction in the risk of hypertension (RR 0.95; 95% CI 0.90 - 1.00) was observed for an increase of 100 mg/day of magnesium intake. However, the results of 4 meta-analyses of RCTs evaluating magnesium supplementation were not consistent. A meta-analysis **(Jee *et al.* 2002)** including 20 studies of hypertensive and normotensive individuals, observed a little reduction in blood pressure but it was not significant. In contrast, Dickinson et al., found a small beneficial effect on blood pressure due to the magnesium supplementation **(Dickinson *et al*. 2006)**. Kass et al., (n = 22 RCTs) reported a reduction of 3 - 4 mmHg on SBP and 2 - 3 mmHg on DBP with oral magnesium supplementation **(Kass *et al.* 2012)**. Finally, Rosanoff et al., reported a more important reduction of 18.7 mmHg on SBP and 10.9 mmHg on DBP in participants with high blood pressure (SBP > 155 mmHg) **(Rosanoff & Plesset 2013)**.

Magnesium can act like a natural blocker of calcium channels in the cells, which is a possible mechanism to explain the reduction on blood pressure. Moreover, sodium and magnesium compete to bind sides on vascular smooth muscle cells. Magnesium also increases the prostaglandin E, binds to potassium in a cooperative manner, induces endothelial vasodilation, improves endothelial dysfunction and decreases intracellular calcium and sodium thus reduces blood pressure **(Houston 2011)**.

III.a.4 Fibers

Observational studies report that a diet high in fiber is associated with a lower risk of hypertension in women **(Witteman *et al.* 1989)** and in men **(Ascherio *et al.* 1992)**. On the other hand, this association is no longer significant in women after adjusting for confounding factors, but it is still significant in men. The cross-sectional ENNS study showed on a representative sample of the French population that a high-fiber diet was associated with lower level of SBP in normotensive individuals **(Vernay *et al.* 2012)**. In addition, a meta-analysis of several randomized trials **(Whelton *et al.* 2005)** reports a significantly reduced blood pressure level by increased fiber intake in hypertensive subjects; in normotensive patients, the reported effect is less important and not significant. This potential beneficial effect of the fibers on BP and the occurrence of hypertension would imply, among other things, their ability to increase insulin sensitivity **(Bessesen 2001)** and a direct effect on endothelial function **(Cleland *et al.* 1998)**. However, it is difficult to assert

an independent protective role for dietary fiber as it improves the intestinal absorption of other minerals such as magnesium, often present in fiber-rich foods **(Coudray *et al.* 2003, Greger 1999)**.

III.a.5 Lipids

The relationship between lipids and blood pressure and, more broadly CVD, depends more on the quality of fat intake than on the total amount of lipids in the diet (**Frisoli *et al.* 2011)**. Indeed, lipid intake include saturated fatty acid (SFAs), intake of polyunsaturated fatty acids (PUFA): omega 3 and omega 6, present in oily fish, and monounsaturated fatty acid intake (MUFAs), present in olive and rapeseed oils. Most cross-sectional observational studies do not report a relationship between BP level and total amount of lipids per day, but a significant association when considering the ratio of saturated fatty acid to mono or polyunsaturated fatty acids **(Grimsgaard *et al.* 1998, Zheng *et al.* 1999, Miettinen *et al.* 1982 and Miura *et al.* 2008)**. It should be noted that a prospective study based on a French population sample **(Dauchet *et al.* 2007)** did not show a significant relationship between lipid intake (in terms of quality) and changes in BP level. Regarding interventional studies, the OMNIHEART trial **(Appel *et al.* 2005)** showed that a diet enriched in lipids (mainly comprising MUFAs), to the detriment of carbohydrate intake, could reduce SBP by 2.9 mmHg. This was subsequently confirmed by a meta-analysis **(Schwingshackl *et al.* 2011)** grouping 9 trials that examined the effect of a diet enriched in MUFAs, and reported an average decrease of -2.26/-1.15 mm Hg for systolic and diastolic BP respectively. Other tests that have studied the effect of omega-3 supplementation on BP levels, give more controversial results: the most recent meta-analysis, reports a significant beneficial effect in hypertensive patients but not in normotensive patients **(Campbell *et al.* 2013)**; on the other hand the effect seems very dependent on the dose. A 2004 meta-analysis of the Cochrane group also concludes that while high-omega-3 diets remain to be promoted, there is no strong evidence that omega-3 supplementation other than dietary supplements is protective of CVD, and furthermore, such supplementation is not devoid of undesirable (digestive) effects at doses considered to be potentially beneficial **(Hooper *et al.* 2004)**. In France, an ancillary analysis of the SU.FOL.OM3 (Folate supplementation and Omega-3) study, a randomized controlled trial that tested the impact of omega3 supplementation (and/or B vitamins) in subjects with a history of cardiovascular disease **(Galan *et al.* 2010)**,

reported no significant effect on BP level in the supplemented group after 5 years **(Szabo *et al.* 2012)**.

The mechanisms by which fatty acids might affect BP are unclear. Indeed, while epidemiological data suggest an adverse effect of SFAs and a beneficial effect of PUFA and MUFA, the experimental data are inconclusive. The most likely hypotheses are that MUFAs could increase the excretion of salt (and water) by a pathway involving prostaglandins and could increase vasorelaxation by inhibiting thromboxane **(Hall 2009)**.

III.a.6 Fruits and Vegetables

Consumption of fruits and vegetables has been consistently associated as a protector factor with CVD and hypertension. A meta-analysis of 9 prospective cohort studies, including 185 676 individuals with a follow-up ranging from 3.8 to 28 years, evidenced an inverse association between the consumption of fruit and vegetables and the risk of hypertension. The consumption of fruit and vegetables was evaluated individually, when they compared the highest with the lowest quintile of consumption, they found a 13% (Relative risk (RR) 0.87; 95% CI 0.79 - 0.95) and 12% (RR 0.88; 95% CI 0.79 - 0.99) lower risk, respectively. Together, consumers of fruit and vegetables had 10% (RR 0.90; 95% CI 0.84 - 0.98) lower risk of hypertension **(Wu *et al.* 2016)**. Fruits and vegetables are food groups source of antioxidants, which could neutralize the effect of oxidative stress and improve endothelial function. It is estimated that 1.7 million lives could be prevented each year if there was an adequate consumption of these foods **(Wang *et al.* 2015)**.

III.a.7 Proteins

The effect of dietary protein intake on blood pressure is not conclusive. Indeed, data from the literature provide divergent results according to the type of study (cross-sectional observational, prospective or randomized trials) and the method of estimating protein intake: dietary surveys versus biomarker assays in observational studies. In fact, it is difficult to conclude on "the effect of total proteins" because the effect of proteins on BP seems to depend partly on the dietary origin of proteins (plant, animal, linked to specific foods containing other micronutrients having an effect on BP: legumes, soya, oilseeds...) and also on the type of macronutrient substituted by proteins in the intervention tests. A 2010 review **(Altorf-van der Kuil *et al.* 2010)** containing the results of 28 observational studies (15 for which the dietary protein intake estimate was based on dietary surveys and 13 for

which it was based on the biomarker assay) and 20 randomized trials, concluded that there is a moderate beneficial effect of total protein intake on BP. In fact, cross-sectional observational studies in which the total protein intake is estimated from dietary surveys do not show either an association or a beneficial association between protein intake and SBP **(Garcia-Palmieri *et al.* 1984, Havlik *et al.* 1990, He *et al.* 1995, Masala *et al.* 2008, Pellum *et al.* 1983, Reed *et al.* 1985, Stamler *et al.* 1996)**, and 3 prospective studies based on dietary surveys are not conclusive **(Stamler *et al.* 2002, Liu *et al.* 1996, Alonso *et al.* 2006)**.

With respect to intervention trials, a meta-analysis of 40 trials assessed the association between a high-protein diet versus a high-carbohydrate diet and the level of BP, reported a significant beneficial effect of a higher protein diet with a mean decrease of -1.76 / -1.15 mm Hg for systolic and diastolic BP respectively **(Rebholz 2012)**. However, in most of the included trials, the caloric load differed between study groups, which may have an effect on the BP level. Finally, the only major trial is the OMNIHEART study, which reported using a constant caloric intake between groups, showed a beneficial effect of a high-protein diet or a diet rich in monounsaturated fatty acids compared to a rich diet in in carbohydrates. Again, it is difficult to conclude whether the benefit is due to increased intake of protein and monounsaturated fatty acids or a decreased carbohydrate intake **(Appel *et al.* 2005)**.
Finally, if we consider the effect of proteins according to their origin, the cross-sectional observational data on BP level or prospective on the risk of hypertension **(Stamler *et al.* 2002, Alonso *et al.* 2006, Wang *et al.* 2008)** are concordant on a beneficial effect of vegetable proteins. Conversely, a recent study combining data from 3 prospective cohorts **(Borgi *et al.* 2015)** showed a significant positive relationship between the consumption of animal proteins from all sources (red meats, poultry but also fish) and the risk of occurrence of hypertension. This study also raises the question of the relationships between proteins and BP according to the cooking method of food, thus introducing an additional potential parameter to be taken into consideration.

The physiopathological explanations of a beneficial effect of proteins on BP level are based on the potential hypotensive effect of certain amino acids: cysteine, glutamate, arginine, leucine, taurine, and tryptophan, which would increase the release of NO (in particular L -arginine) and have a direct effect on RAAS **(Vasdev & Stuckless 2010, Dong *et al.* 2011)**.

III.b Global dietary pattern

- **DASH**

Research testing the effects of an overall dietary pattern on blood pressure was based on the fact that other dietary factors could influence BP at a time where non-pharmacological recommendations to prevent and treat hypertension included reduction of salt intake and possible increasing dietary potassium as the only nutritional approaches. This idea was supported by observational studies reporting that intake of magnesium, potassium, calcium, fiber, and protein was significantly associated with lower BP. However, intervention trials that tested these nutrients, often as dietary supplements, found the reduction in blood pressure small and inconsistent. This discrepancy in the results led investigators to conduct the Dietary Approaches to Stop Hypertension (DASH) trial that tested the effects of dietary patterns on BP, rather than individual nutrients **(Appel *et al.* 1997)**. DASH tested the combined effects of nutrients that occur together in food. The trial included 459 participants randomly distributed in the following three groups for 8 weeks: (a) control diet, (b) diet rich in fruits and vegetables, (c) combination diet, i.e., diet rich in fruits and vegetables and reduced in saturated fats and low-fat dairy products (DASH-combination diet), the salt intake was kept constant in all three groups. **Table 5** presents the nutrient and food intake of each diet and the nutritional analysis of the diets actually provided. At the end of trial, it was observed that the reduction in both systolic and diastolic blood pressure was greater in the combination diet group, the results of the DASH trial after 8 weeks are as follows:

- The decrease in BP for the participants in the DASH diet group was -5.5 / -3 mmHg (for the SBP ($p < 0.001$) and for the DBP ($p < 0.001$) respectively) compared to that of the participants in the control group and -2.7 / -1.9 mm Hg (for SBP ($p = 0.001$) and for DBP ($p = 0.002$) respectively) compared to the group "diet rich in fruits and vegetables".
- BP decline in participants in the "high fruit and vegetable diet" group was -2.8 / -1.1 mmHg (for SBP ($p < 0.001$) and for DBP ($p = 0.07$), respectively) compared to the control group.

In addition, the combination diet lowered both systolic and diastolic BP more in hypertensive patients 11.4/5.5 mmHg than in normotensive individuals 3.5/2.1 mmHg **(Appel *et al.* 1997)**. Investigators of the trial suggested that a DASH combination diet might be an effective nutritional approach in the prevention and management of hypertension.

Since then, the effectiveness of DASH diet has been established through DASH trials conducted in different parts of the world **(Saneei *et al.* 2014),** mostly using a DASH score constructed based on food groups described by Fung and colleagues **(Fung *et al.* 2008)**. A recent meta-analysis, including 17 trials, reports a mean hypotensive effect of the DASH diet of -6.74 / -3.59 mmHg for SBP and DBP respectively, with a great heterogeneity between studies with respect to the composition the diets, the hypertensive status of the subjects, whether weight loss was associated with the diet and the duration of the trials **(Saneei *et al.* 2014)**. Finally the subgroup analyzes confirm an effect of the DASH diet independent of weight loss and sodium consumption. As in the original study, the effect of the DASH diet is greater in hypertensives (mean decrease of -6.82 / -3.59 mmHg for SBP and DBP respectively) than in normotensive patients (-2.44 / -1.69 mmHg for SBP and DBP respectively). A recent OMNIHEART Trial (Optimal Macronutrients Intake to Prevent Heart Disease Trial) conducted on 2195 participants reported the additional benefit of replacing the carbohydrate content of DASH diet either with proteins or monounsaturated fats (preferably from vegetable source). OMNIHEART-like diet resulted in BP reduction of 3.9/2.2 mmHg **(Molitor *et al.* 2014)**.

- **Adherence to DASH in epidemiologic studies**

Following these observations, epidemiological studies have subsequently investigated the relationship between adherence to a DASH-diet and its effect on the BP and risk on hypertension. Results of these studies are not in accordance. In fact, a prospective study conducted in a population of women in the US found no association between adherence to a DASH type diet, and incidence of hypertension **(Folsom *et al.* 2007)**. However, the association was found in the Nurses Health Study cohort also done on a female population in the US **(Forman *et al.* 2009)**. In Europe, the benefit of adherence to a DASH regimen on BP level or the risk of developing hypertension has been reported in several epidemiological studies **(Schulze *et al.* 2003, Harrington *et al.* 2013)**. Surprisingly, in a study conducted in Spain, only adherence to the DASH regime and not adherence to a Mediterranean diet was associated with a decreased risk of hypertension **(Toledo *et al.* 2010)**. More recently, prospective analysis from a large cohort of healthy French adults "NutriNet-Santé Cohort", reported associations between incidence of hypertension and several nutrient and food groups such as sodium, potassium, fruits and vegetables, and fibers. In addition, adherence to the DASH-style diet was strongly inversely associated with incident hypertension: (Q4 versus Q1) HR=0.66 (95% CI, 0.58–0.75) **(Lelong *et al.* 2017)**.

Table 5. Intake of nutrient and food groups in the different groups of the DASH trial* (Appel *et al.* 1997).

ITEM	CONTROL DIET		FRUITS AND VEGETABLES DIET		COMBINATION DIET (DASH)	
	Nutrient Target	Menu Analysis#	Nutrient Target	Menu Analysis#	Nutrient Target	Menu Analysis#
Nutrients						
Fat (% of total kcal)	37	35.7	37	35.7	27	25.6
Saturated	16	14.1	16	12.7	6	7.0
Monounsaturated	13	12.4	13	13.9	13	9.9
Polyunsaturated	8	6.2	8	7.3	8	6.8
Carbohydrates (% of total kcal)	48	50.5	48	49.2	55	56.5
Protein (% of total kcal)	15	13.8	15	15.1	18	17.9
Cholesterol (mg/day)	300	233	300	184	150	151
Fiber (g/day)	9	NA	31	NA	31	NA
Potassium (mg/day)	1700	1752	4700	4101	4700	4415
Magnesium (mg/day)	165	176	500	423	500	480
Calcium (mg/day)	450	443	450	534	1240	1265
Sodium (mg/day)	3000	3028	3000	2816	3000	2859
Food groups (no. of servings/day)						
Fruits and juices		1.6		5.2		5.2
Vegetables		2.0		3.3		4.4
Grains		8.2		6.9		7.5
Low-fat dairy		0.1		0.0		2.0
Regular-fat dairy		0.4		0.3		0.7
Nuts, seeds, and legumes		0.0		0.6		0.7
Beef, pork, and ham		1.5		1.8		0.5
Poultry		0.8		0.4		0.6
Fish		0.2		0.3		0.5
Fat, oils, and salad dressing		5.8		5.3		2.5
Snacks and sweets		4.1		1.4		0.7

DASH-diet emphasizing on 8 components: high consumption of fruits, vegetables, whole grains, low-fat dairy foods, legumes and nuts, and low intake of sodium, sweetened beverages, and red and processed meat.

* Values are for diets designed to provide an energy level of 2100kcal.

Values are the results of chemical analyses of the menus prepared during the validation phase and during the trial. NA denotes not available.

- **Mediterranean Diet**

A study conducted in the Mediterranean region in 1950 reported that the people living in this region live longer and have less CVS diseases as compared to other European regions. This finding prompted further research on the lifestyle and dietary habits of the people living there. The main features of Mediterranean diet (MD) are **(Trichopoulou *et al.* 1997)**:

- Increase intake of fruits, vegetables, and pulses,
- High consumption of monounsaturated fatty acids and polyunsaturated fatty acids,
- Less consumption of red meat,
- Restricted intake of alcohol.

The diet of the Mediterranean countries is not amended in a kind of diet rather characterized by common everyday food choices. Major food choices in MD are fruits, vegetables, nuts, seeds, wine, fish, legumes, cereals, bread, milk, olives, and olive oil which are rich in fiber, phenols, flavonoids, isoflavones, phytosterols, and plant acids that are important bioactive ingredients and contribute to the metabolism. In addition, fish, olives, and olive oil are rich in MUFA, PUFA, and phytochemicals (polyphenols, alpha-tocopherol), which have pleiotropic beneficial effects on the cardiovascular and nervous system.

The effects of a MD were seen in a 6-year follow-up study involving 9408 males and females that reported that strict implementation of a MD resulted in reduction in SBP by 3.1 mmHg and DBP by 1.9 mmHg. On the other hand, moderate compliance resulted in 2.4 mmHg reduction in SBP and 1.3 mmHg reduction in DBP **(Núñez-Córdoba *et al.* 2008)**. The effects of a MD were further evaluated in a meta-analysis of 50 clinical trials that found that a traditional MD to be associated with 2.35 mmHg reduction in SBP and 1.58 mmHg reduction in DBP **(Kastorini *et al.* 2011).**

The mechanisms by which MD impacts BP levels are not fully understood. There is more likely a multifactorial beneficial effect rather than an effect of one major nutrient. It appears that the adoption of eating habits such as those of the MD may have preventive and therapeutic effects against hypertension and other CVD. However, other factors that characterize the peoples of the Mediterranean such as physical activity, exposure to sun, and fresh seasonal products should be also considered.

In summary, studies that have examined the effect of a healthy overall diet such as the DASH diet or the MD have an effect on BP greater than that of any individual nutrient and are in favor of a synergistic effect of the nutrients consumed concomitantly.

"Healthy" diets associated with improved BP levels combine a diet rich in fruits and vegetables, oilseeds, whole grains and low in saturated fats and red meats.

The BP reduction from a healthy overall diet is greater in hypertensive subjects than in normotensive subjects. If the results of the randomized controlled trials agree on this hypotensive effect, epidemiological data from observations have more divergent results. This difference in effect can be explained by:

- Cultural differences limiting the adherence to certain diets promoting dietary habits of different regions,
- Gene-environment interactions (and in the specific case feeding) different according to the populations
- The difficulty of maintaining particular eating habits in "real life"

III.c Physical activity

Physical activity is defined as any bodily movement produced by contraction of skeletal muscles that increases energy expenditure above resting levels. In this context, physical activity comprises routine daily tasks such as commuting, occupational tasks, or household activities, as well as purposeful health-enhancing movements/activities **(Caspersen *et al.* 1985)**. Studies demonstrating the protective effects of physical activity on hypertension were initially published in the late 60's **(Paffenbarger *et al.* 1968)**. Since then, accumulating data exist on this association. In fact, epidemiological studies have demonstrated an inverse relationship between physical activity and hypertension **(Lesniak & Dubbert 2001)**; some results also suggest a dose-response relationship **(*Warburton et al. 2010)***. Even modest levels of physical activity have been associated with a decrease in the risk of incident hypertension **(Hayashi *et al.* 1999)**. A meta-analysis of 54 randomized controlled trials involving 2419 participants revealed that ≥ 150 min exercise/week resulted in decrease in both systolic and diastolic BP by 5.13/2.78 mmHg, respectively, 121–149 min/week exercise resulted in 4.67/2.11 mmHg reduction, and ≤ 120 min/week exercise resulted in 2.82/2.19 mmHg reduction **(Whelton *et al.* 2002)**. Of note that the terms "physical activity", "exercise", and "physical fitness" are related, but they are used differently in the literature. Most studies have evaluated the effects of physical activity as exercise/sports on hypertension. Exercise can be divided into "aerobic" exercise (walking, cycling) and "resistance" training designed to improve muscular strength and/or endurance. Resistance exercises can be dynamic or isometric (like weightlifting). Randomized trials suggest that the best form of physical activity conveying BP-lowering benefits is aerobic exercise (5– to 7–mm Hg reduction) **(Dimeo *et al.* 20012)**, but dynamic and isometric resistance exercise are also effective. Meta-analysis of 28 randomized controlled trials involving 1012 individuals divided in 33 subgroups revealed that dynamic resistance training exercise resulted in reduction of both systolic and diastolic blood pressure by 2.6/3.11 mmHg respectively as compared to a non-training control group; similarly, isometric handgrip training resulted in 11.8/5.8 mmHg reduction in both systolic and diastolic blood pressure as compared to the non-training control group **(Cornelissen *et al.* 2011)**. The mechanisms of physical activity in preventing hypertension are unclear, but may include decreased cardiac output, diminution of sympathetic nervous system and renin-angiotensin system activity, decreased total peripheral vascular resistance and insulin resistance, and improved endothelial function **(Arakawa 1993)**. In addition, a

recently conducted research study reported that aerobic exercise induced 20% increase in NO release from vascular endothelial cell and 10% decrease in blood pressure **(Zago *et al.* 2010)**.

As physical activity takes many forms, it has been measured in a variety of ways in experimental, interventional and epidemiological research. There exist more than 30 different instruments for self-reported physical activity (Pereira et al. 1997) and accurate measurement of physical activity mostly rely on calculating the EE **(Lagerros & Lagiou 2007)**. This is done through using a questionnaire gathering the type of the activity which is assigned a specific Metabolic Energy Turnover (MET) value (intensity) obtained from reference lists **(Ainsworth *et al.* 1993, Ainsworth *et al.* 2000)** and the duration. The energy expenditure is obtained (in kcals or MET hours) using the formula is shown in **Figure 7** and can be further categorized into low, medium, high or very high. Physical activity is an important modifiable factor associated with hypertension, but the diversity of the instruments used in epidemiologic studies, important questions remain, such as type and amount of activity required for a protective effect, as well as whether there are critical time periods when physical activity is more important.

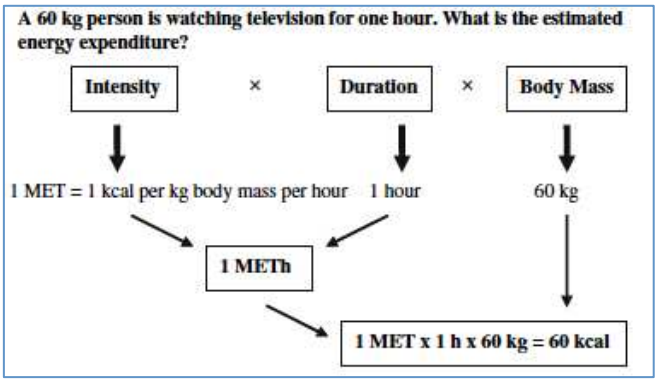


Figure 7. Energy expenditure (in kcals or MET hours) as a function of absolute intensity, duration and frequency of physical activity
MET= metabolic energy turnover

III.d Alcohol consumption

The relationship between alcohol consumption and BP is still controversial in the literature; particularly regarding to the amount of alcohol intake, choice of beverage, pattern of drinking and differences among sexes. Indeed, epidemiologic evidence suggests that heavy alcohol consumption is strongly associated with increased risk of hypertension **(Fuchs *et al.* 2001, Tsuruta *et al.* 2000)**. However, the effects of light to moderate alcohol intake on BP remain unclear and debatable. In fact, one randomized controlled trial involving 491 participants for 5 months showed a dose-dependent relationship between alcohol consumption and BP level and revealed that individuals who consume ≥ 350 ml alcohol/week had their systolic and diastolic BP 5.8/2.9 mmHg higher than non-drinkers, individuals who consumed 160–349 ml alcohol/per week had their systolic and diastolic BP 4.5/2.2 mmHg higher than non-drinkers, similarly, the individuals who consumed less than 160 ml alcohol per week had their systolic and diastolic BP 3.7/5.2 mmHg higher than non-drinkers **(Arkwright *et al.* 1985)**. On the other hand, a prospective analysis of the effect of alcohol use on the occurrence of hypertension in women participating in the Nurse's Health Study and men belonging to the Physician Health Study **(Sesso *et al.* 2008)** confirmed that heavy alcohol intake increases hypertension risk but the association between light-to-moderate alcohol intake and the risk of developing hypertension differed in women and men. In addition, the threshold only above which there is an association differs; among men, the relationship was more linear up to a dose of 40 g/d, after which the risk of development of hypertension appears to plateau, while in women, a possible J-shaped association was reported, in which light-to-moderate alcohol consumption modestly lowered hypertension risk. A meta-analysis of 16 prospective studies including 33,904 men and 193,752 women found similar results **(Briasoulis *et al.* 2012)** and reported that heavy alcohol consumption more than 20 g/day is associated with the risk of development of HTN in both women and men, while moderate drinking (5 to 10 g/d) had a trend toward increased risk of HTN in men and a decreased risk in women.

Furthermore, studies examined the influence of the pattern of alcohol consumption. The INTERSALT study, found that heavy drinkers with great variation in their daily alcohol consumption (i.e., episodic or binge drinkers) showed the greatest variation in BP, compared with abstainers or even daily heavy drinkers **(Marmot *et al.* 1994)**. Indeed, ambulatory BP demonstrated a rapid onset/offset of elevated BPs in weekend drinkers, with baseline ambulatory BP being 2.4 mm Hg higher on Monday than on Thursday **(Rakic**

***et al.* 1998)**. Additional evidence also suggests that drinking outside of meals appears to have a significant effect on hypertension risk, independent of the amount of alcohol consumed. Drinkers who consumed alcohol separately from food had a 64% greater risk of hypertension **(Stranges *et al.* 2004)**. The multifactorial nature of alcohol consumption and its association with BP elevation and hypertension development merits further evaluation especially in the presence of discrepant results.

III.e Smoking

Smoking is a major risk factor for atherosclerotic CVD and cancer. Despite the great number of observations showing the certainty of cardiovascular damage from smoking, findings from epidemiologic studies on the effect of smoking on BP are inconclusive. It is not clear if smoking exposure causes a rise or reduction of blood pressure and, otherwise, also if the occurrence of hypertension in smokers is a consequence of the greatest number of hypertensive people independently from smoking, or smoking actively contributes to changes in BP **(Leone 2011)**. Findings using ambulatory BP monitoring have shown that both normotensive and untreated hypertensive smokers present higher daily BP values than non-smokers **(Groppelli *et al.* 1992)**, while others refer to a lowering **(Hughes *et al.* 1993)** or to no chronic effect **(Primatesta *et al.* 2001)** of smoking for office BP, which is not lowered by smoking cessation.

This discrepancy could be explained as follows. Initially, a vasoconstriction mediated by nicotine causes acute but transient increase in SBP. This phase is followed by a decrease in BP as a consequence of depressant effects played chronically by nicotine itself. Simultaneously, carbon monoxide is acting directly on the arterial wall causing, in the long run, structurally irreversible alterations **(Trap-Jensen 1988, Hill & Wynder 1974)**. At this time, there is a change in BP that increases again, and often constantly, its levels following chronic exposure **(Leone 2005)**.

In addition, smoking influences the metabolic steps of all major classes of drugs commonly used for the treatment of hypertension reporting changes in response to antihypertensive drugs in hypertensive smokers **(Leone 2011)**. Thus, affecting the efficacy of treatment independently by the mechanism of action or choice of antihypertensive drugs. As such, smoking cessation could help in the management and control of hypertension.

More recently, epidemiologic studies describe that the relationship between smoking and BP is influenced by age, race, lifestyle factors and amount and type of tobacco smoking.

Nevertheless, beside the impact on BP values, smoking is a powerful CV risk factor and smoking cessation is probably the most effective lifestyle measure for the prevention of cancer and CVDs including stroke, myocardial infarction and peripheral vascular disease **(Doll *et al.* 1994, Lims *et al.* 2012)**.

III.e Psychological stress

Psychosocial stress is another lifestyle risk factor that has been shown to contribute to high blood pressure **(Kaplan & Nunes 2003)**. Early studies found weak or inconsistent evidence, but new evidence have emerged suggesting that chronic exposure to psychological stress can cause increased blood pressure and lead to hypertension development **(Linden & Moseley 2006)**. The effects of chronic stress are being investigated in a number of domains—including work, marriage, low socioeconomic status and early-life violence. Associations between these domains and BP outcomes have been reported, but the evidence varies. A cohort study of over 3,000 young adults 9 showed that urgency/impatience behavior, and hostility assessed during young adulthood were strongly associated with a higher risk of developing hypertension 15 years later **(Yan *et al.* 2003)**. Similarly, a meta-analysis of six prospective studies comprising 34,556 subjects aged between 18 and 64 years **(Gasperin *et al.* 2009)** showed that individuals who had stronger responses to stressor tasks were 21% more likely to develop blood pressure increase when compared to those with less strong responses (OR: 1.21; 95%CI: 1.14- 1.28; $p < 0.001$). Some studies mentioned that associations of psychological stress and elevated BP were different by gender **(Steptoe & Willemsen 2004)**. In a cross-sectional study conducted in China **(Hu *et al.* 2015)**, general stress contributed approximately 9.1% (95% CI [3.1, 15.0]) to the risk for hypertension, but after adjustment for risk factors, women showed a greater risk of hypertension if they had either stress at work or at home: OR = 1.285, 95% CI (1.027, 1.609) and OR = 1.231, 95% CI (1.001, 1.514), respectively. However, this increased risk for hypertension by stress was not found in men.

Additionally, it has been suggested that therapies such as relaxation or meditation, may help to reduce the effects of stress, thereby reducing BP **(Linden & Moseley 2006)**. In this context, a systematic review of 23 treatment comparisons from 17 randomized trials conducted in patients with elevated blood pressure, demonstrated strong effects of transcendental meditations on reductions in blood pressure **(Maxwell *et al.* 2007)**.

The impact of stress on the development of hypertension is believed to involve a sympathetic nervous system response, leading to acute elevations in BP, but the process by which stress contributes to sustained BP elevation over time is not well understood **(McEwen 1998)**. In the presence of available evidence, it is important that future epidemiologic studies evaluate the role of stress with its different forms and triggers on BP and hypertension.

III.f Anthropometric measurements

- **Overweight, obesity and body mass index**

Data from the literature provide strong evidence of the association between body weight and high BP and of a direct relationship between overweight/obesity and hypertension **(Harsha & Bray 2008)**. This association has been seen in different population. Obesity may be responsible for about 40% of hypertension in the Nurses' health Study **(Huang *et al.* 1998)** and even higher accounting for 78% in men and 65% in women of the risk for primary hypertension in the Framingham Offspring Study **(Hubert *et al.* 1983)**. Similarly, the French Nutrition and Health Survey [Etude Nationale Nutrition Sante´ (ENNS)] carried out among a representative sample of the French population, found that obese individuals had a higher prevalence of hypertension and an increased likelihood of antihypertensive drug use. After adjustment, obesity was associated with a 62% lower risk of BP control (OR: 0.38, 95% CI: 0.19–0.75) compared with the lean/normal-weight status **(Czernichow *et al.* 2012)**. Recent prospective data described obesity to be linked with incident HTN **(Shuger *et al.* 2008)**.

Furthermore, epidemiological studies have consistently identified a direct relationship between body mass index (BMI) and BP that is continuous and almost linear, with no evidence of a threshold **(Hall 2003, Jones *et al.* 1994)**. Alternatively, weight reduction is associated with decreased BP; in a meta-analysis of randomized controlled trial, an average weight loss of 5.1 kg was associated with mean SBP and DBP reductions of 4.4 and 3.6 mmHg, respectively **(Neter *et al.* 2003)**. Moreover, studies reporting hypertension after bariatric surgery support this latter as an accepted treatment for obesity; a meta-analysis of 3 studies, reported long-term hypertension remission rates (define as BP <140/90 mmHg without medication) of 38.2% after gastric bypass and 17.4% after a gastric band **(Puzziferri *et al.* 2014)**.

In addition, the relationship between obesity at a young age and change in obesity status over time and future risk of hypertension has been studied. An analysis of data from 4 prospective studies in 6,328 persons that measured childhood and adult body mass index with a follow-up of 23 years demonstrated that overweight or obese children who were obese as adults increased the risk of hypertension 2.7 times **(Juonala *et al.* 2011)**. Obese childrene who became normal weight adults had reduced the risk of developing hypertension to a level similar to persons who were never obese **(Juonala *et al.* 2011)**.

The mechanisms by which obesity leads to hypertension are illustrated in **Figure 8**. It seems mainly related to an increased in cardiac output as a result of overactivation of the renin–angiotensin–aldosterone system **(Engeli & Sharma 2001)**, involvement of the sympathetic nervous system, and inhibition of functional effects of natriuretic peptides on vasodilation and natriuresis **(Reisin & Jack 2009)**. These metabolic mechanisms could also contribute to understand why obese individuals exhibit a lower BP control despite a higher likelihood of treatment use **(Muntner *et al.* 2004, Egan *et al.* 2010)**.

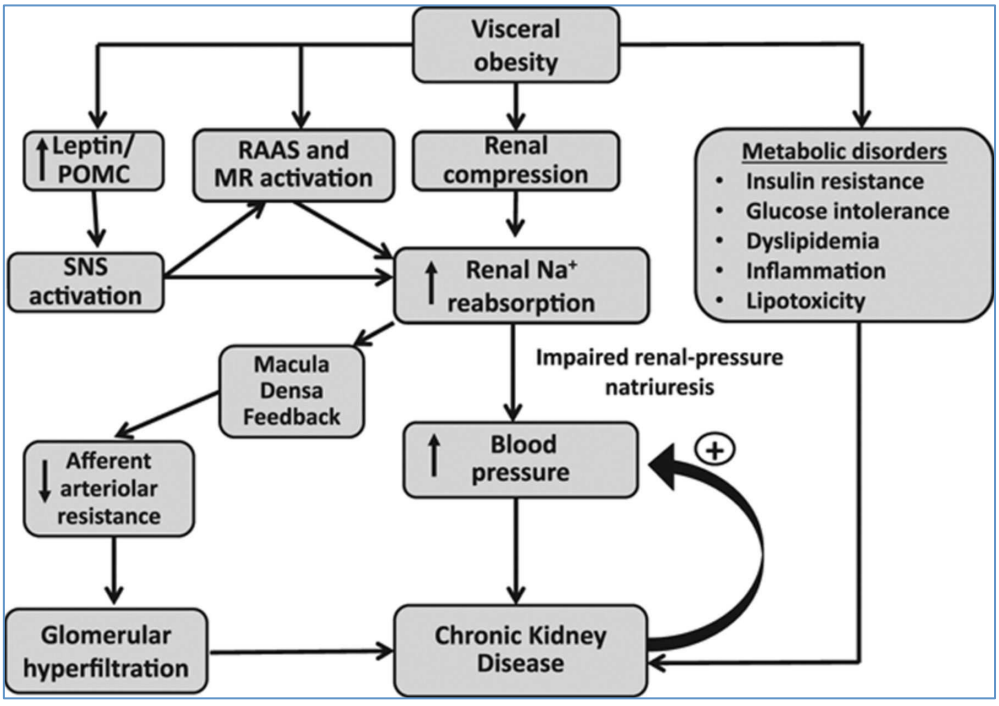


Figure 8. Summary of mechanisms by which obesity initiates development of hypertension and renal injury (Hall *et al.* 2015).
MR=mineralocorticoid receptor; POMC= proopiomelanocortin; RAAS= renin–angiotensin–aldosterone system; and SNS=sympathetic nervous system.

III.g Other factors

III.g.1 Diabetes

Hypertension is a comorbidity that is frequently associated with diabetes. Approximately 20% - 60% of diabetics suffer from hypertension; this variation depends mainly on factors such as the degree of obesity, age and sex **(Arauz-Pacheco *et al.* 2004)**. Diabetes also increases the risk of a coronary event, in men it doubles, and in women it quadruples **(Arauz-Pacheco *et al.* 2004)**. The incidence of hypertension in type II diabetics is 1.5 to 3 times higher than in non-diabetics **(Sowers 2003)**. Blood pressure increases in diabetics due to weight gain and insulin resistance, in addition, to the activation of the sympathetic nervous system, as well as the angiotensin-renin system and increased vascular resistance **(Sowers 2004)**.

III.g.2 Hypercholesterolemia

Hypercholesterolemia is defined as a concentration greater than 200 mg/dl cholesterol in the blood **(Hall 2001)**, a known risk factor for cardiovascular disease. Fatty deposits called atheromatous plaques, located in the arteries walls, trigger a series of processes that end in atherosclerotic formation and reduce the arteries' diameter, increase peripheral resistance, and consequently, blood pressure **(Rafieian-Kopaei *et al.* 2014)**. Several studies have shown an association between dyslipidemia and the risk of hypertension **(Haffner *et al.* 1996, Sesso *et al.* 2005)**. The Physicians' Health Study, after 18.6 years of follow-up, observed that participants in the highest quintile of total cholesterol had 23% higher risk of hypertension (RR 1.23; 95% CI 1.01 - 1.50) compared to those in the first quintile. The same behavior was observed in participants in the highest quintile of non- HDL (high density lipoprotein) cholesterol they had 39% (RR 1.39; 95% CI 1.13 - 1.70) higher risk of hypertension. In contrast, participants in the highest quintile of HDL cholesterol had less risk of hypertension (RR 0.68; 95% CI 0.56 - 0.84) compared to those in the first quintile **(Halperin 2006)**.

IV. Magnitude of the effect of lifestyle factors on hypertension

IV.a Summary of the magnitude of the individual effect of lifestyle factors

As described above, modifiable risk factors, particularly nutritional and lifestyle factors influence BP and the development of hypertension. This association is well established for some factors but remains unclear for others.

A summary of the effect of nutritional factors and lifestyle factors on BP and the associated level of evidence, based on the above literature review, is presented in **Table 6** below.

Table 6. Blood pressure effect (decrease or increase) and level of evidence of different nutritional and lifestyle factors

Factor	Effect on BP	Level of Evidence
Excessive salt intake	Increase	++
Calcium intake	Decrease	±
Vitamin D supplementation	Decrease	±
Potassium intake	Decrease	++
Magnesium intake	Decrease	±
Fibers	Decrease	±
Saturated fatty acids	Increase	±
Mono-unsaturated fatty acids	Decrease	+
Poly-unsaturated fatty acids	Decrease	+
Fruits and vegetables	Decrease	+
Proteins animal source	Increase	+
Proteins vegetable source	Decrease	+
DASH diet	Decrease	++
Mediterranean diet	Decrease	+
Physical activity	Decrease	++
Alcohol consumption	Increase	++
Smoking	Increase	±
Psychological stress	Increase	+
Overweight and obesity	Increase	++

++ indicate an association with a strong level of scientific evidence based on randomized trials, meta-analyses
+ indicate a probable association with observational data views or clinical trials
± indicate a possible association but with inconclusive or discordant literature data

IV.b Summary of the magnitude of the combined effect of lifestyle factors

In addition to the individual BP effect of lifestyle factors, a number of studies evaluated the effect of a combination of 2 or more factors on the BP. Data from the literature describe the beneficial BP lowering effect when combining several factors, most frequently, the effect is considered sub-additive to their effect individually (**TOHP II Collaborative Research Group 1997, Kumanyika *et al.* 2005, Stevens *et al.* 2001, Miller *et al.* 2002**). For example, the DASH-Sodium study evaluated the effect of sodium reduction in addition to a DASH diet on BP level in pre-hypertensive and hypertensive subjects. In this study, subjects who had reduced sodium intake and a DASH diet had a greater blood pressure lowering effect than those with reduced sodium intake or a DASH diet alone **(Vollmer *et al.* 2001)**. The ENCORE study evaluated the additive effect of lifestyle behaviors on the BP in untreated overweight hypertensive individuals **(Blumenthal *et al.* 2010)**. The study and found that the addition of exercise and weight loss to the DASH diet resulted in larger BP reductions than DASH diet alone (12.5/5.9 vs. 7.7/3.6 mmHg, respectively; p<0.001). The PREMIER trial also assessed the effect of a combination of lifestyle modifications on diet. In the PREMIER trial, 810 with above-optimal BP including stage-I hypertensive patients who were not receiving any hypertensive medication were randomized into three groups **(Appel *et al.* 2003)**:

- Advise only/control group
- Established, implementing: weight loss, improved fitness, lowered sodium intake
- Established plus DASH diet group: increased fruits, vegetables and dairy intake

Table 7 describe reductions in SBP and DBP in hypertensive and non-hypertensive patients from baseline to 6 months as well as hypertension prevalence and optimal BP rates

Table 7. Blood pressure reductions from the PREMIER trial (Appel *et al.* 2003)

	Hypertensive		**Non-hypertensive**		**Overall**			
	SBP reduction	DBP reduction	SBP reduction	DBP reduction	SBP reduction	DBP reduction	Prevalence of HTN*	Optimal BP^
Established n = 268	12.5 (11.5)	5.8 (7.0)	9.4 (9.1)	5.3 (6.5)	10.5 (10.1)	5.5 (6.7)	17%	30%
Established plus DASH diet group n =269	14.2 (10.1)	7.4 (7.1)	9.2 (9.3)	5.8 (6.6)	11.1 (9.9)	6.4 (6.8)	12%	35%
Advise only/control group n=273	7.8 (10.3)	3.8 (7.1)	5.8 (8.4)	3.8 (5.8)	6.6 (9.2)	3.8 (6.3)	26%	19%

Reductions of BP are presented in mean (SD) mmHg; DBP=diastolic blood pressure, SBP=systolic blood pressure, HTN=hypertension; SD=standard deviation; DASH=dietary approach to stop hypertension

*In comparison to the baseline hypertension prevalence of 38%

^Optimal blood pressure defined as SBP <120 mmHg and DBP <80 mmHg DBP

Similarly, two randomized control trial of non-pharmacological interventions were conducted to find out the combined effect of Na+ restriction and weight loss on the blood pressure. Both studies compared 3 intervention groups to a control group/usual care group. Although the 3 intervention groups showed a BP lowering effect, the BP decrease observed in the combination group was lower than the sum of the BP lowering effect of the low-salt group alone and the weight-reduced group alone **(TOHP II Collaborative Research Group 1997, Whelton *et al.* 1998)**. The BP reductions in the different groups in both studies are summarized in **Table 8**. Of note that the TONE study was conducted on elderly hypertensive patients receiving treatment, while the TOHP II study included pre-hypertensive untreated individuals. This illustrates the beneficial BP lowering effect, yet sub-additive, of a combination of factors in treated and untreated individuals. Lastly, Miller et al. also reported the beneficial effect of a combination of weight reduction, combined with exercise and a healthy diet in treated individuals **(Miller *et al.* 2002)**.

Table 8. Net mean blood pressure reductions compared to usual care (control) group in the TONE and TOHPII studies

	TONE study		**TOHPII study**	
Participants	Elderly treated hypertensive individuals		Overweight or obese pre-hypertensive subjects	
	SBP reductions	**DBP reductions**	**SBP reductions**	**DBP reductions**
Dietary Na+ restriction alone group	3.4 mmHg	1.9 mmHg	2.9 mmHg	1.6 mmHg
Weight loss alone group	4.0 mmHg	1.1 mmHg	3.7 mmHg	2.7 mmHg
Combination of Na+ restriction and weight loss group	5.3 mmHg	3.4 mmHg	4.0 mmHg	2.8 mmHg

DBP=diastolic blood pressure, SBP=systolic blood pressure;

From an epidemiologic perspective, the combined effect of the non-pharmacologic measures recommended in guidelines was recently studied. One study used prospective data to evaluate the combined impact of normal weight, physical activity, limited alcohol consumption and adoption of a healthy diet, on the incidence of hypertension **(Lelong *et al.* 2019)**. This study found that compared with adhering to 0, 1, 2 or 3 healthy lifestyles, adhering to all of them was found associated with a reduction of the hypertension risk of half (HR = 0.55 [95% CI, 0.46–0.65]). Interestingly, this study has similar objective to one of the objectives of this thesis and it will be interesting to compare both results.

V. Non-pharmacological recommendations for the prevention and treatment of hypertension

Current worldwide guidelines for the prevention and management of hypertension emphasize non-pharmacological therapy also termed "lifestyle modification". Expert committees developed the guidelines while relying on data from the literature with recommendations based on strong level of evidence aimed for specific population. Non-pharmacological therapy is fundamentally important approach to prevention and management of high BP, either on their own or in combination with pharmacological therapy. Alone, lifestyle modification can especially be useful for the prevention of hypertension such as in adults with elevated BP. Along with drug therapy they can be sufficient to meet goal BP in managing patients with stage 1 hypertension, and they are an integral part of the management of persons with stage 2 hypertension. Non-pharmacological interventions can be accomplished by means of behavioral strategies aimed at lifestyle changes, they are effective in lowering BP, with the most important interventions being weight loss, adopting the DASH (Dietary Approaches to Stop Hypertension) diet, reducing sodium intake, increasing dietary potassium supplementation, increasing physical activity, and limiting alcohol consumption. Various other non-pharmacological interventions have been reported to lower BP, but the extent and/or quality of the supporting clinical trial experience is less persuasive. Some differences in the recommendation are found between guidelines. **Table 9** presents the different non-pharmacological measures of recently published international guidelines:

- The 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 **(Whelton *et al.* 2018).**
    - *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines*
- 2018 ESC/ESH Guidelines for the management of arterial hypertension (**Williams *et al.* 2018).**
    - *The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)*

Table 9. Lifestyle interventions for patients with hypertension or high-normal BP in American and European guidelines (Whelton *et al.* 2018, Williams *et al.* 2018).

Intervention	Recommendation	ACC/AHA	ESC/ESH
Dietary sodium	Reduce dietary sodium intake	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults	Salt restriction to <5 g per day is recommended
Weight/body fat	Weight loss	- Best goal is ideal body weight - Aim for at least a 1-kg reduction in body weight for most adults who are overweight. - Expect about 1 mm Hg for every 1-kg reduction in body weight.	- Body-weight control is indicated to avoid obesity BMI >30 kg/m2 or waist circumference >102 cm in men and >88 cm in women), - Aiming at healthy BMI (about 20–25 kg/m2) and waist circumference values (< 94 cm in men and <80 cm in women) to reduce BP and CV risk
DASH dietary pattern	Healthy diet	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	- Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil) - Low consumption of red meat; - Consumption of low-fat dairy products are recommended.
Alcohol consumption	Moderation in alcohol intake	In individuals who drink alcohol, reduce alcohol† to: • Men: ≤2 drinks daily • Women: ≤1 drink daily	It is recommended to restrict alcohol consumption to: • Less than 14 units per week for men. • Less than 8 units per week for women It is recommended to avoid binge drinking
Exercise	Increase physical activity	Aerobic: • 90–150 min/wk • 65%–75% heart rate reserve Dynamic resistance: • 90–150 min/wk • 50%–80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set Isometric resistance • 4 × 2 min (hand grip), 1 min rest between exercises • 30%–40% maximum voluntary contraction, 3 sessions/wk • 8–10 wk	Regular aerobic exercise (e.g. at least 30 min of moderate dynamic exercise on 5–7 days per week) is recommended.
Dietary potassium	Enhanced intake of dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium	N/A
Smoking	Smoking cessation	N/A	Smoking cessation, supportive care, and referral to smoking cessation programs are recommended.

DASH = Dietary Approaches to Stop Hypertension; SBP = systolic blood pressure; N/A = not available; BMI = body mass index; BP = blood pressure; CV = cardiovascular

†In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

Interestingly, these recommendations, which are based on data with a high level of evidence (generally demonstrated by randomized trials), give recommendations that may be different for similar populations (hypertensive individuals). Indeed, both guidelines agree on a salt restriction, but the threshold differs from 3.75g/day (American guidelines) to <5g/day (European guidelines). Similarly, recommendations on weight "aim" a healthy BMI (20–25 kg/m2) in the ESC/ESH guidelines while ideal body weight is set as the "best goal" or even modest weight loss in ACC/AHA guidelines. Furthermore, physical activity is detailed according to type and frequency of exercise in the ACC/AHA guidelines and dietary potassium intake is strongly recommended (3500-5000mg/day) and achieved by the DASH diet. The European guidelines did not elaborate on the influence of potassium intake and BP only mentioning, "increased potassium intake is associated with BP reduction and may have a protective effect, thereby modifying the association between sodium intake, BP, and CVD." Of note, the 2018 Canadian guidelines for the treatment of hypertension provide health behavior management recommendations that are generally in accordance with the American guidelines, except that stress management is a non-pharmacolgic intervention that should be considered for whom stress might be contributing to high BP **(Nerenberg *et al.* 2018)**.

With regards to France, the prevention of hypertension is one of the objectives of the National Health and Nutrition Program (PNNS), which is a public health plan aimed at improving the health status of the population by acting on one of the its major determinants: nutrition (i.e dietary habits) and physical activity. The PNNS thus published nutritional recommendations for the prevention of chronic diseases and particularly cardiovascular risk factors. These recommendations are available in **Appendix 1** and **Table 10** presents the nutritional and food habits recommendations. Of note that the PNSS issued recommendations particularly aiming at the prevention of high blood pressure. Here, in addition to nutritional and food recommendations, they emphasize on increase physical activity, weight reduction, reduce salt intake to 6.9-8g/day and increase potassium food intake through the increase in the consumption of fruit and vegetables. The recommendations bring importance to the sodium / potassium ratio, that should be lowered to <2 (**Synthèses du PNNS 2006**).

In addition, the French society of hypertension published guidelines for the management of hypertension in adults and recommended the implementation and

monitoring of nondrug measures for all hypertensive adults. These measures are **(Blacher *et al.* 2013)**:

- Reduce excessive consumption of salt
- Take up regular physical activity
- Reduce weight if overweight
- Reduce excessive consumption of alcohol
- Adopt a diet rich in fruit and vegetables
- Cease smoking

Table 10. Nutritional recommendations issued by PNNS for the general population

	Recommendation*
1. Fruits and vegetables	At least 5/d
2. Bread, cereals, potatoes and legumes	At each meal according to appetite
3. Whole grain food	Choose whole grains and whole grains breads more often
4. Milk and dairy products	3/d ≥ 55-years old : 3 to 4/d
5. Meat, poultry seafood and eggs	1 to 2/d
6. Seafood	At least 2/week
7. Added fat	Limit consumption
8. Vegetable added fat	Favor fat of vegetable origin
9. Sweetened foods	Limits consumption
10. Non-alcoholic beverages	Drink water as desired Limit sweetened Beverages: no more than 1 glass/d
11. Alcoholic beverages	Women advised to drink ≤2 glasses of wine/d and ≤3 glasses/d for men
12. Salt	Limit consumption

PNNS= National Health and Nutrition Program (programme national nutrition santé)

In conclusion, non-pharmacological therapy derived from worldwide guidelines for the prevention and management of hypertension include diet, salt intake, potassium intake, alcohol consumption, physical activity and weight. However the quantitative or qualitative targets for each of these measures differ across the guidelines. This heterogeneity makes their promotion more challenging and justifies the need to conduct further studies evaluating their impact in specific populations in order to provide further evidence of their efficacy to possibly modify and improve the recommendations if necessary. In addition, the recommendations emphasize lifestyle changes based on intervention trials that are especially effective in hypertensive individuals. Hence, the study of their effect in terms of primary prevention or improving BP control in hypertensive treated individuals remains necessary.

CHAPTER 2: OBJECTIVES

Summary and Objectives

I. Summary and purpose

Hypertension is the most prevalent chronic disease worldwide and a major risk factor of cardiovascular diseases. With such an increasing prevalence and associated disease burden, it has become a global major public health issue. Hypertension has a multifactorial origin that includes genetic and behavioral factors. Different lifestyle behaviors have been shown to be associated with the prevalence of hypertension. On this basis, non-pharmacological measures are recommended within worldwide guidelines, with the aim of preventing and improving the risk of complications related to high BP. In addition, research suggests that their combination has a sub-additive effect on BP reduction. However, it appears to be difficult to implement and maintain these lifestyle behaviors in daily life. In addition, differences in the recommendations between the guidelines justifies the need to conduct further studies evaluating their impact in order to provide further evidence of their efficacy. Studies evaluating different populations are needed, particularly to determine the relationship between lifestyle factors and incident or prevalent or uncontrolled hypertension.

Additionally, limited epidemiologic data on HTN exist in Lebanon, an upper-middle-income country with a surface area of 10 542 Km2 and a population of 6.007 million (2016). In fact, one previous study reported that the prevalence of HTN and BP control were 35.9% and 27%, respectively **(Matar *et al.* 2015)**. However, the study had several limitations: (1) the study population was not representative of the Lebanese population having an over-representation from Beirut district, (2) it did not extensively discuss the risk factors associated with HTN, and (3) it did not address the relationship between HTN and lifestyle behaviors, including dietary habits.

While in France, data on hypertension is more widely available, yet the presence of large population-based studies such as the French CONSTANCES cohort study presents a major opportunity to provide further data on the determinants of hypertension and particularly from a non-pharmacologic perspective.

From an epidemiological standpoint, updated data describing the epidemiology of hypertension are warranted in both countries, at a nation-wide level. A quantification of the

individual and combined effect of lifestyle factors on hypertension and uncontrolled blood pressure deserves further evaluation.

The purpose of this thesis is to study the risk factors associated with hypertension at the population level and to evaluate the relationship between non-pharmacological risk factors and hypertension. In particular the aim is to investigate the influence of an unhealthy behavior on blood pressure and the magnitude of the individual and combined effect of lifestyle factors on hypertension.

II. Objectives of the thesis

The objectives of the thesis that led to published or submitted articles are the following:

1. To determine the prevalence and risk factors of hypertension in the Lebanese adult population. Particularly, to evaluate the association between HTN and lifestyle behaviors as well as to explore the relationship between the Lebanese-adopted Mediterranean diet and psychological factors on the systolic BP (Article 1).

2. To examine the individual and combined associations between unhealthy behaviors, specifically, non-adherence to dietary recommendations, low physical activity, overweight, and heavy alcohol consumption, with hypertension from the CONSTANCES study. Also, to evaluate the quantitative extent to which modifiable lifestyle factors are determinants of **hypertension**, assessing the magnitude of potential primary prevention (Article 2).

3. To examine the individual and combined associations between unhealthy behaviors - as mentioned above - with uncontrolled hypertension. Similarly to the second objective, the aim is to evaluate the quantitative extent to which modifiable lifestyle factors are determinants of **uncontrolled hypertension,** in order to assess the magnitude of their effect in the management of hypertension, from a gender-based perspective (Article 3).

4. To assess sociodemographic, clinical and behavioral predictors of uncontrolled hypertension among treated hypertensive individuals from the CONSTANCES cohort French study (Article 4).

CHAPTER 3:
MATERIALS AND METHODS

Materials and Methods

This chapter will provide details about the materials and methods used to achieve the objectives. First, the Lebanese study conducted on a sample representative of the Lebanese population will be described. It served to answer the first objective related to prevalence and determinants of hypertension at the Lebanese population level. A focus was made on dietary and psychological factors. Then the French CONSTANCES cohort study will be described, mentioning its objectives, details concerning protocol approval, data acquisition and analysis. Different population will be studied: all enrolled individuals and those with known hypertension receiving anti-hypertensive therapy. Focus was given to lifestyle factors, unhealthy behavior and association with hypertension and uncontrolled hypertension. Finally, the statistical analyses used will be described.

I. Methods: Lebanese sample

I.a Study design and population

The main framework of the study was to assess the prevalence of cardiovascular diseases and their risk factors among Lebanese residents. We conducted a cross-sectional study between September 2013 and October 2014, using a multistage cluster sample all over Lebanon. We randomly selected 100 circumscriptions from the list of circumscriptions in Lebanon (villages, towns, and cities) **(Central Administration of statistics 2005)**. Then, using a software program, residents aged 20 years and above were randomly selected from the list of dwellers provided by the local authority, with no a priori exclusion criteria. Several teams consisting each of at least one medical doctor or trained medical students have scheduled visits for a face-to face interview with the participants at a local governmental authority. Participants were asked to bring with them on the date of the interview, their medications and if available any laboratory tests done in the previous year. After giving written consent, data were gathered. During the interview, individuals diagnosed with learning disabilities or psychiatric disorders were finally not included. The study was funded by "Fondation-Institut de Recherche Medicale: F-MRI" which is a public utility and non- profit organization regulated by the Swiss law.

The sample size was initially calculated according to the framework of the study

assessing the prevalence of CVD. We used Epi Info™ (Center for Disease Control, Atlanta, GA, USA. Available from: http://wwwn.cdc.gov/epiinfo/). Since no other figure was available, we used the prevalence of hypertension of 23.1% among individuals aged ≥30 years as the reference **(Tohme *et al.* 2005)**; we took into account a worst acceptable result of ±4% difference with the aforementioned prevalence and a 95% confidence interval (CI) as well as the two-stage sampling design, a minimal sample size of 1,285 was required. The study included 2,088 individuals and is to date, one of the largest studies done in Lebanon.

I.b Selection of study participants

In order to determine the prevalence of hypertension, all enrolled participants were included in the analysis except:

- 40 individuals for missing the majority of the data
- 23 for missing blood pressure values
    - BP measures were needed in order to determine elevated BP and thus could influence the prevalence rate of hypertension.
- 11 for using vasoactive medications
    - α (1)-adrenergic receptor blockers for benign prostatic hyperplasia treatment
    - These medications have BP lowering effect, thus influencing the observed BP measurements and consequently hypertension prevalence rate. In other words, these could false negatively lead to lower BP values, masking hypertension.

Accordingly, 2014 participants were included in the analysis (**Figure 9**)

I.c Data collection

For every individual, the following measurements were performed during the interview at the governmental location: BP, glycemia, height and weight, and waist circumference. In addition, standardized questionnaires were used to gather information and were prepared in English. They were translated into Arabic by an independent translator and checked by the investigators; a back translation by another translator was done to ensure lack of discrepancy between English and Arabic versions. The questionnaires were pretested in a pilot sample of 20 individuals for finalization of details. The questionnaire consisted of the following parts:

- General questions gathering socio-demographic characteristics:
    - Age, gender, marital status, education, type of work, income per month, and region of residence

- Health status using questions to self-report:
    - History of cerebrovascular disease, cardiovascular disease and presence of angina using the Angina Rose questionnaire
    - History of hospitalization
    - Family history
    - Present chronic diseases
- Medication use
    - Self-reported current medications used and regimen
    - Medication adherence using self-reported questionnaire, the eight-item Morisky Medication Adherence Scale
- Women's health
    - Contraceptive and hormone therapy
- Pollution
    - Using questions gathering information about exposure to indoor and outdoor pollution
- Smoking habit
    - Determining use of tobacco products (cigarette, water pipe, cigar, pipe)
    - Questions related to quantity and duration of cigarette smoking and waterpipe (hooka/chicha) smoking
- Alcohol consumption was determined
    - Frequency of intake
- Nutrition
    - Using a 21-item food frequency questionnaire about consumption of certain food groups adapted to the Lebanese diet **(Issa *et al.* 2014)**
    - Frequency ranged from: never, 1-2 times/day, 3-6 times/day, at every meal
- Physical activity
    - Using questions gathering type, frequency and duration of the activity/sports/exercise
- Perceived stress and quality of life was assessed using 3 questionnaires
    - The 22-item Beirut distress scale **(Barbour *et al.* 2012)**
    - Short form-12 (SF-12) questionnaire **(Ware *et al.* 1996)**
    - The MacNew Heart Disease health-related quality of life questionnaire **(Deaton *et al.* 1998)**

Of relevance to the first objective, we used: Demographic and socioeconomic data, history of self-reported chronic diseases and medication use, lifestyle behaviors (cigarette and water pipe smoking, alcohol consumption and frequency and duration of exercise), dietary habits, and psychological stress.

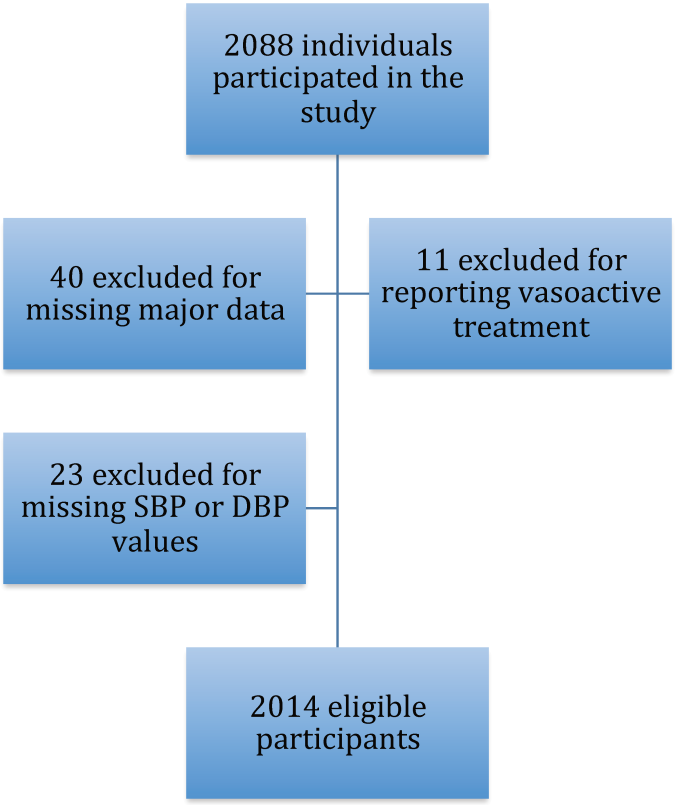


Figure 9: Flow chart presenting study population of the Lebanese analysis.

I.d Blood pressure measurements and definitions

- **BP measurements**

BP measurements were taken using standardized protocol. Standard procedures define the medical device specifications and detail the measurement methods of each type of data; of particular importance are BP measurements in this case. This ensures the successful replication of data collection for all volunteers regardless of when, where and by whom they are performed. BP measurements were taken as such: SBP and DBP were measured twice at 1-minute interval in a seated position after 5 minutes of rest. The average of the 2 measurements was used for the analyses. When the SBP measurements differed by more than 20mmHg and the DBP by more than 10mmHg, a third measurement was taken after at

least 5 more minutes and the average of the last 2 measurements was used. Pulse pressure (PP = SBP −DBP) and mean arterial pressure (MAP = 2/3 * DPB + 1/3 *SBP) were calculated according to the usual formula.

- **Hypertension definition**

Prevalent HTN was defined by a SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg or by individuals who were currently taking antihypertensive medications according to the 2018 European guidelines **(Williams *et al.* 2018)**. As such, definition of cases with prevalent hypertension took into consideration the following variables:

1. Do you have hypertension? (yes/no)
2. Do you take a medication for high blood pressure? (yes/no)
3. Self-reporting antihypertensive therapy including any of:
    a. Calcium channel blockers (CCB), angiotensin receptor blocker (ARB), angiotensin converting enzyme (ACE) inhibitor, thiazide or thiazide like diuretic, beta-blockers, diuretic including any of loop, potassium sparing or aldosterone receptor blocker.
    b. A detailed list of anti-hypertensive medication listed by pharmacological class and generic name is found in **Appendix 2**
4. BP measurements SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg

The following cases were possible and prevalent hypertension was defined accordingly:

1) Participants who reported being hypertensive but were not taking blood pressure lowering drugs and their average SBP or DBP did not meet the above definition were **not** considered to be hypertensive.
2) Participants reporting not having hypertension (answering "No" to the question do you have hypertension?) and receiving a medication to lower their blood pressure were considered to have prevalent hypertension.
3) Participants reporting not having hypertension and not receiving a medication to lower their blood pressure BUT were taking an anti-hypertensive medication for another probable pathology were considered to have prevalent hypertension.
4) Participants reporting not having hypertension and not receiving a medication to lower their blood pressure and were taking an anti-hypertensive medication for another pathology BUT having a SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg were considered to have prevalent hypertension.

Scenario number 3 can influence (increase) the prevalence of hypertension. In fact we assumed those not reporting having hypertension or being treated for hypertension, yet receiving a BP-lowering medication for the treatment of other disease, as having hypertension. We considered these patients as having hypertension because, their pathology could have been as a results of hypertension (without being aware of having hypertension). For example patients receiving beta-blocker for history of previous myocardial infarction may have had hypertension without their knowledge. For this reason these patients were considered to have prevalent hypertension.

Furthermore, individuals with poor BP control or uncontrolled BP were determined if having a mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg, definition also based on the 2018 ESC/ESH Guidelines for the management of arterial hypertension **(Williams *et al.* 2018)**. The following control rates were determined:

1) Uncontrolled hypertension in treated individuals: defined as those who were receiving anti-hypertensive medication for the treatment of hypertension or for other pathology, yet, their BP was still above the goal, meaning having SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg.
2) Unaware of having hypertension: defined as those not receiving anti-hypertensive medications, but their BP is elevated, that is having SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg
3) Overall uncontrolled hypertension: defined as both cases above. In other words, all those with SBP ≥140 mm Hg and/or a DBP ≥90 mmHg whether receiving anti-hypertensive medication or not were considered in the overall uncontrolled rate.
4) Controlled hypertension on the other hand was considered for those controlled on treatment; that is receiving anti-hypertensive medication and their BP is <140/90 mmHg. Those not receiving anti-hypertensive medications and having SBP<140 and DBP<90mmHg were considered not having hypertension

Figure 10 and Figure 11 present the algorithm for defining and determining the prevalence and control rates of hypertension, respectively.

Figure 10. Algorithm for defining prevalent cases of hypertension in the Lebanese cohort

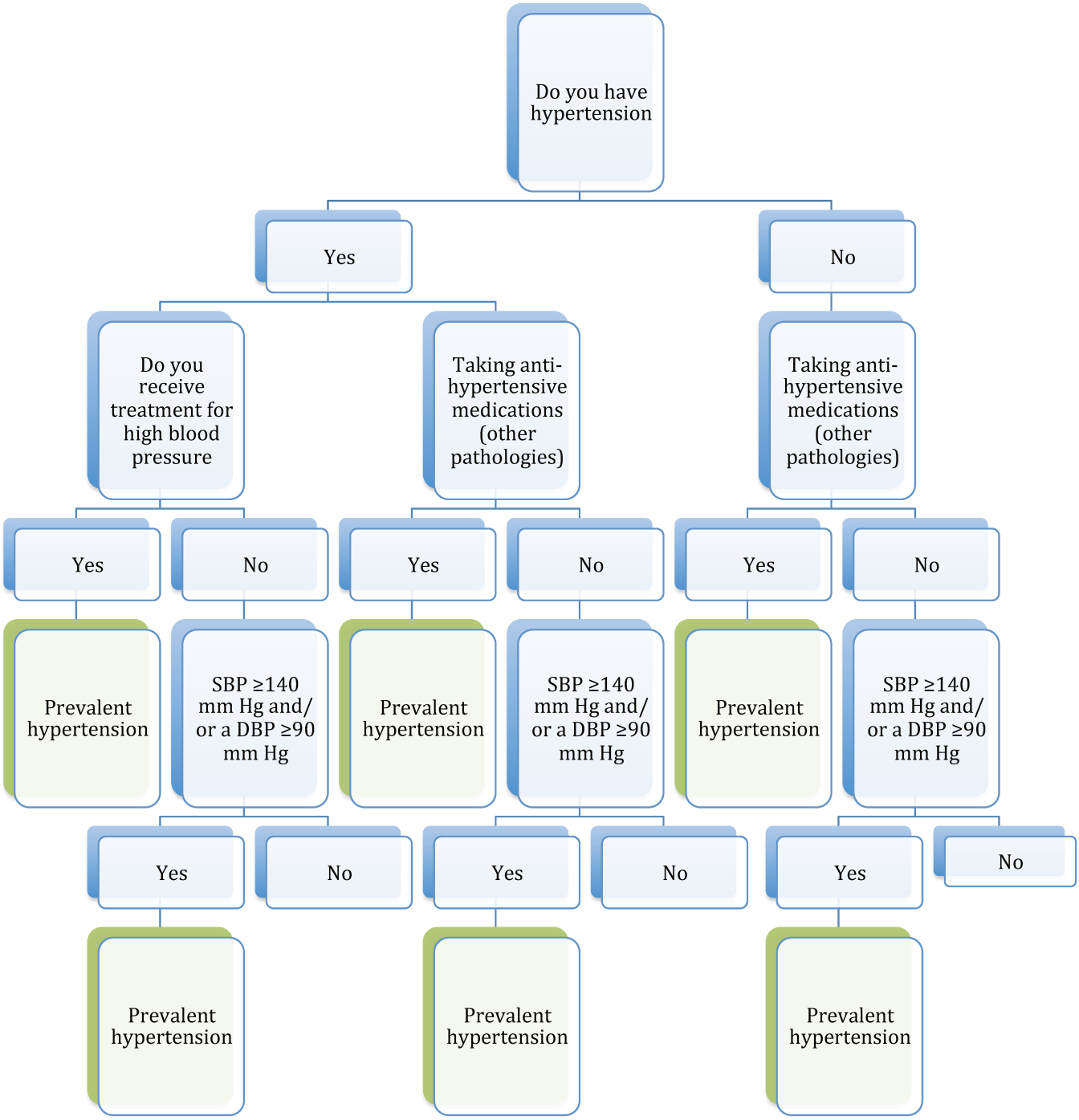
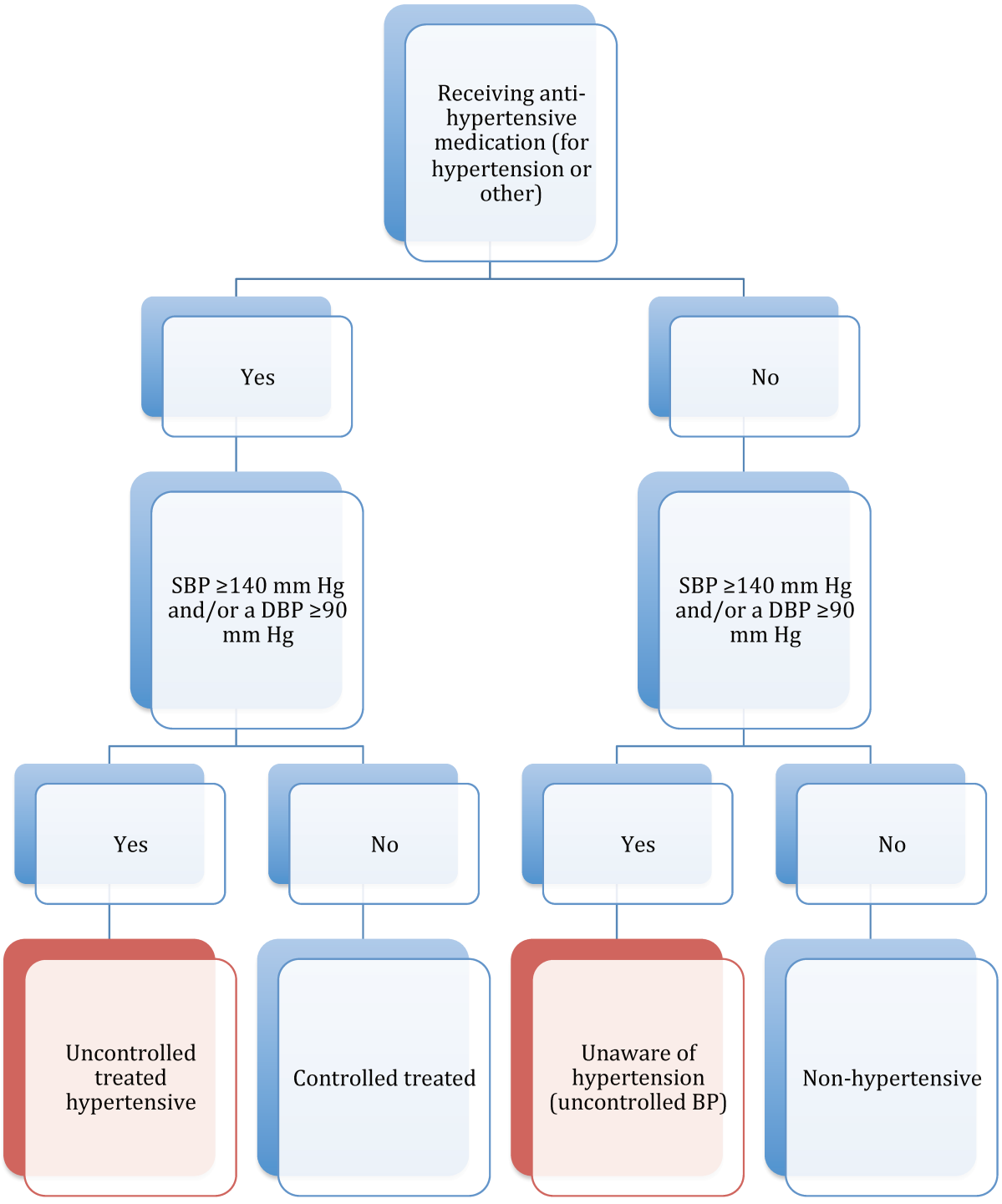


Figure 11. Algorithm for defining uncontrolled hypertension in the Lebanese cohort



Red: overall uncontrolled rate

I.e Socio-demographic characteristics

Of the socioeconomic factors gathered, we classified marital status into: single, married or divorced/widowed. Level of education was categorized into 3 levels: primary-complementary, secondary and university or higher. Income, identified as household income, was classified taking into consideration minimal country wedge and the different possible ranges were: more than 2,000,000 Lebanese pounds (LBP), between 1,000,000-2,000,000 LBP, between 500,000-1,000,000 LBP and <500,000 LBP. Moreover, working status was described as working, retired or unemployed. Lastly, region of living was identified as rural or urban.

I.f Anthropometric measurements and lab tests

Biologic tests included random capillary blood glucose (RCBG) and anthropometric measurements weight, height and waist circumference.

1. RCBP was measured using Accu-Check® Performa (Roche Diagnostics GmbH, Mannheim, Germany).
2. Weight measurement was performed with an electronic scale with participants wearing light clothes; height was measured with a wall-mounted measuring rod. BMI was calculated by dividing weight, in kilograms, by height, in square meters, and reported as a continuous variable as well as divided into three categories:

- Normal weight (BMI <25 kg/m2)
- Overweight (BMI 25 kg/m2 <30 kg/m2)
- Obese (BMI ≥30 kg/m2)

3. Waist circumference was measured using a tape measure, at a level midway between the lower border of the costal margin (the lowest rib) and uppermost border of the iliac crest with cut offs of > 102 cm for men and > 88 cm for female associated with abdominal obesity **(Williams *et al.* 2018)**.

I.g Medical history and health data

Previous medical history was self-reported. Chronic disease were defined accordingly:

- Diabetes was defined as RCBG >200 mg/dL or self reported medication use for glucose control **(Stern *et al.* 2002)**.
- Hypercholesterolemia or hypertriglyceridemia were considered when participants reported having a blood test that diagnosed the condition or if they were taking lipid-lowering medications.

- Coronary heart disease (CHD) was defined as any self-reported history of myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass graft or angina using the "definite angina" definition of the Rose Angina Questionnaire **(Rose 1962)**.
- Cerebrovascular accident (CVA) was determined if participants reported a history of stroke or transient ischemic attack.
- We computed the variable any cardiovascular disease (Any CVD) as those with either CHD or CVA.
- A family history of premature CVD was defined as a fatal or non-fatal CVD event or/and established diagnosis of CVD in a first-degree relative (father, mother, brother, sister, children) before the age of 55 years for males and 65 years for females **(Massimo *et al.* 2016)**.

I.h Lifestyle behavior characteristics

I.h.1 Physical activity

Physical activity (PA) is one of the most important lifestyle factors known to be associated with hypertension. Hence its accurate measurement and assessment is of utmost importance. We used a standard questionnaire to calculate leisure time physical activity on the basis of mean metabolic equivalents (MET) for reported activities and their frequency and duration in MET- min per week; a higher score indicated greater activity **(Ainsworth *et al.* 2000)**. Information was obtained about habitual leisure time physical activity. Questions included type and frequency of sports or recreational activities, whereby the corresponding MET value was based on the updated Compendium of Physical Activities [such as bicycling (MET = 8), basketball (MET = 8), and walking for exercise (MET = 4)] and lessons [such as swimming (MET = 6), dance (MET = 6.5), and stretching (MET = 2.5)]. That is, leisure time activities were considered as those requiring energy expenditure above that required for daily living activities. The physical activity score was computed by multiplying an estimate of the MET for each recorded activity by the weekly frequency with which it was performed and an overall average weekly score was calculated as MET*times per week. Time spent on each activity was multiplied by the MET value of the activity. The resulting METmin products were summed to produce an index of daily physical activity.

Then physical activity level was classified as follow:

- Light-intensity physical activity (1.6–2.9 METmins),

- Moderate-intensity physical activity (3–5.9 METmins)
- Vigorous-intensity physical activity (≥ 6 METmins)

The use of the MET as an assessment of physical activity is commonly done in epidemiologic data and therefore is considered a reliable instrument, which allows our results to be compared to the data found in the literature.

In addition we considered individuals to be physically active according to the WHO definition, if they were regularly involved in moderate-intensity physical activity for at least 150 min per week or vigorous intensity physical activity for 75 min at least per week. Otherwise, individuals were considered to have insufficient physical activity **(WHO, Global Recommendations on Physical Activity for Health 2010)**.

I.h.2 Alcohol consumption

Alcohol consumption was determined using 4 questions, identifying alcohol drinkers and then assessing the overall frequency of alcohol use (everyday, occasionally, none) and over the past 12 months. We did not gather information regarding the type and amount of beverages neither about the drinking pattern. Previous epidemiologic studies conducted in Lebanon suggested that alcohol intake is under-reported by participants because of religious considerations **(Issa *et al.* 2014)**. Therefore assessment of alcohol consumption may be subject to bias.

I.h.3 Smoking status

Smoking status took into consideration the use of any tobacco product including cigarettes, cigar, pipe and waterpipe. It was important to assess waterpipe smoking (also known as hubble-bubble, hookah, shisha or narguileh) because of it popular use in Lebanon. In fact, in Lebanon, the prevalence of waterpipe smoking has increased extensively, reaching 15% among Lebanese adults in general, and 35.9–51.9% among males and females 40 years of age or older, respectively **(Akl *et al.* 2011, Salameh *et al.* 2011)**. Excessive smoking has been noticed too, with about 36.5% of exclusive Lebanese waterpipe smokers who smoke more than seven waterpipes per week **(Waked *et al.* 2009)**. Lebanon is considered the first country in comparison with other countries in regard to current waterpipe smoking among school students (25%) and is the second after Pakistan among university students (28%) **(Akl *et al.* 2011)**. Waterpipe smoking continues to be a popular pastime across the country despite its significant health risks. Recent studies conducted on waterpipe smoking have

found a strong association with cancer **(Shihadeh & Saleh 2005)** and respiratory diseases **(Kiter *et al.* 2000)**. Even more recently some data exits about a link with cardiovascular diseases and stroke **(El-Hajj *et al.* 2019)**, but data on hypertension are lacking. In this context, evaluation of waterpipe smoking on hypertension could yield some interesting findings and will add data to the literature.

Smoking status was categorized as current smoker, ex-smoker and non-smoker. Current smokers were defined as individuals who smoked cigarette and/or waterpipe in the previous 12 months and those who had quit within the past year. Participants who had quit more than a year earlier were considered former smokers. For those identified to have ever smoked, cumulative dosing of cigarettes was calculated as the average number of daily packs multiplied by the corresponding duration of smoking (pack × years), while that of waterpipe was calculated as the mean number of weekly waterpipes multiplied by the duration of smoking (waterpipe × years) **(Salamé *et al.* 2012)**.

I.i Lebanese Mediterranean Diet Score computation

We used a food frequency questionnaire (FFQ) to evaluate dietary habits. The FFQ was a 21-item questionnaire with food groups derived from the traditional Mediterranean Diet, but adapted to the Lebanese food, hence the term the Lebanese Mediterranean Diet. A Lebanese Mediterranean Diet Score (LMDS) based on a priori positive and negative components was derived from the FFQ. The LMDS calculation in our analysis was conducted similarly to a previous study computing and validating the LMDS. However this method of scoring underwent some modifications compared to that of the previously and widely used Mediterranean diet score **(Trichopoulou *et al.* 2003)**. First, because the FFQ used in this study was non-quantitative, the LMDS was based on intake frequencies instead of median intake in grams. Second, nuts were not included in the LMDS because they were most often consumed salted and oil roasted in the study sample. Third, for fat intake, olive oil intake frequency was used, because it is the only fatty substance to be commonly used by Lebanese population separately from cooking. Finally, ethanol consumption was not accounted for in the score computation, as it is believed that alcohol would be, if consumed, largely underreported because of religious prohibitions against consumption **(Issa *et al.* 2014)**.

The choice of negative components to be included in the LMDS also showed some differences compared to the initially developed Mediterranean diet score **(Trichopoulou *et al.* 2003)**, namely fried potatoes or chips, sweets and fast food were added as detrimental

food. The rationale behind including the latter food categories was based on a previous study **(Salameh *et al.* 2014)**, showing that these items were all included in the "Western type food" dietary pattern which was inversely associated with the "plant food" dietary pattern in both the "vegetarian/low calorie diet" cluster and the "westernized diet" cluster. According to the rationale of the Mediterranean dietary pattern **(Willett *et al.* 1995)**, the intake frequencies of the following 14 food categories were included in the diet score **(Issa *et al.* 2014)**.

- The intake frequency options were: never, two times or less per week, three to six times per week, at least 1 time per day and at all meals
- Beneficial components were: raw vegetables, cooked vegetables, fruits, olive oil, grains, beans, fish, rice and pasta, brown bread or crackers, and white bread or crackers
- Detrimental components were: meat, fried potatoes or chips, sweets and fast food

Then, based on previously described Mediterranean scores **(Panagiotakos *et al.* 2006, Panagiotakos *et al.* 2007)**, monotonic functions were used in order to score the consumption frequency of these food categories. For components presumed to be beneficial, a score of 0 was assigned for people who did not consume it at all, a score of 1 was assigned for those who consumed it three to six times per week, a score of 2 for those who consumed it at least twice a week, a score of 3 for those who consumed it at least once per day and a score of 4 for those who consumed it at every meal. For components presumed to be detrimental, an inverse score was assigned. People who consumed it at every meal were assigned a score of 0, those who consumed it at least once a day were assigned a score of 1, those who consumed it at least twice a week, a score of 2, those who consumed it three to six times a week, a score of 3 and those who did not consume it at all, a score of 4. As for dairy products, fruit juice and carbonated beverage, they were not included in the scale because the questionnaire did not specify whether they were consumed full fat or low fat, natural or artificial, with sugar or artificial sweeteners, respectively **(Issa *et al.* 2014)**. Thus, the LMDS score ranged from 0 (minimal adherence to the traditional Lebanese Mediterranean diet) to 52 (maximal adherence). As such, higher score indicates better dietary quality. The score was not calculated for those with more than 2 missing responses of the LMDS variables, whereas those with one or 2 missing responses had a score over 48 and 44 respectively that was converted to a score over 52.

I.j Beirut Distress Scale

As discussed in chapter 1, recent studies established a relationship between the effect of psychological stress and BP level as well as on the risk of hypertension. Furthermore the Canadian guidelines on hypertension recommend stress management for whom stress might be a contributor to high BP **(Nerenberg *et al.* 2018)**. Therefore evaluating psychological stress in epidemiologic studies is imperative. Although the questionnaire used 3 different instruments that can evaluate psychological distress, we decided to consider in our analysis the Beirut Distress Scale (BDS-22), which is a scale that was developed and validated in the Lebanese population. In fact, the MacNew questionnaire is a valuable tool for assessing and evaluating health related quality of life in patients, particularly, with heart disease **(Höfer *et al.* 2004)** and is not commonly used in the literature in studies on hypertension. Similalry, the SF-12, which is a multipurpose short form survey with 12 questions, is limited by the complexity of its use and its scoring strategy. Actually, the scoring method requires questions (grouped) to be combined, scored, and weighted to provide psychometrically based physical component summary and mental component summary scores as well as an overall health-related-quality of life score. Also, this tool is not specific for psychological health. Furthermore both the MacNew and SF-12 instruments require permission to be used in epidemiologic studies **(Ware *et al*. 1996, Deaton *et al.* 1998).**

The BDS-22 consists of 22 items that involves six factors, reflecting: depressive symptoms, demotivation, psychosomatic symptoms, mood deterioration, intellectual inhibition and anxiety. Adequate internal consistency and test-retest reproducibility were stated; both factors and the total scale correlated adequately with SRQ-20, SF-36 (psychological component), GHQ-12, MHI-5 and WHO-5 scales **(Barbour *et al.* 2012)**. Although these devices are considered valuable tools, the BDS-22 scale had the advantage to be validated for the Lebanese population. Examples of questions included in the questionnaire are: "You feel despaired", "You think life has no meaning", "You lost the desire to learn", "You isolate yourself" Responses to the questions had a four-point Liker type format: never, little, moderate and much. For each question, a score of 0, 1, 2, 3 was assigned for responses consecutively from "never" to "much". Thus, the BDS-22 ranged from 0 to 66 with higher score indicating higher psychological distress **(Barbour *et al.* 2012)**.

II. Methods: The cohort study CONSTANCES

II.a Study design and population

- **Presentation of CONSTANCES**

CONSTANCES is a general-purpose, population-based prospective cohort designed to contribute to the development of epidemiologic research. It is intended to serve as an open epidemiological research infrastructure accessible to the scientific community for conducting ancillary projects on a variety of research questions with particular interest in occupational and social factors, on chronic diseases and aging **(Zins *et al.* 2010)**.

CONSTANCES cohort also aims to provide useful public health information to the public health authorities and health care regulatory bodies in order to contribute to a better knowledge of the health and health care resource utilization of the French population. Details concerning study design of CONSTANCES are found at www.constances.fr and in the scientific protocol found at http://www.constances.fr/assets/pdf/Scientific-protocol-01-2015.pdf. A summarized description is presented below.

- **Study design and Population**

CONSTANCES has partnered with the National Health Insurance Fund administered by the ''Caisse Nationale d'Assurance Maladie des Travailleurs Salariés'' (CNAMTS). As such, the source of CONSTANCES's population is that of the people in France whose health insurance is administered by the CNAMTS. Health insurance is compulsory in France, and all salaried workers and their families are affiliated to this fund, which covers more than 80% of the French population (approximately 50 million people), but excluding agricultural and self-employed workers that are affiliated to other health insurance funds. As one of the main objectives of CONSTANCES is to provide information on the health status and disease burden of the large part of the French adult population, the CONSTANCES cohort will include adults aged 18-69 at inception randomly selected from the CNAMTS following a sampling scheme stratified on age, sex, socioeconomic status and region of France to ensure a representative sample of the CNAMTS **(Zins *et al.* 2015)**. The CONSTANCES study started in 2012 and by summer of 2019 it included 200,000 volunteer participants.

In France, everyone with health insurance from CNAMTS, as well as their dependents, is entitled to receive free health examinations that include extensive work-ups conducted in Health Screening Centers (HSCs). A total of 110 HSCs are located in France conducting

approximately 500,000 health examinations annually. CONSTANCES, included participants in 22 selected HSCs located in 19 ''departments'' in different regions of France (**Figure 12**). The selected HSCs have experience with recruiting large number of people and with participating in epidemiological studies. All are large, have a staff motivated to work in epidemiology, and use advanced medical equipment; their geographic distribution represents the principal regions of France.

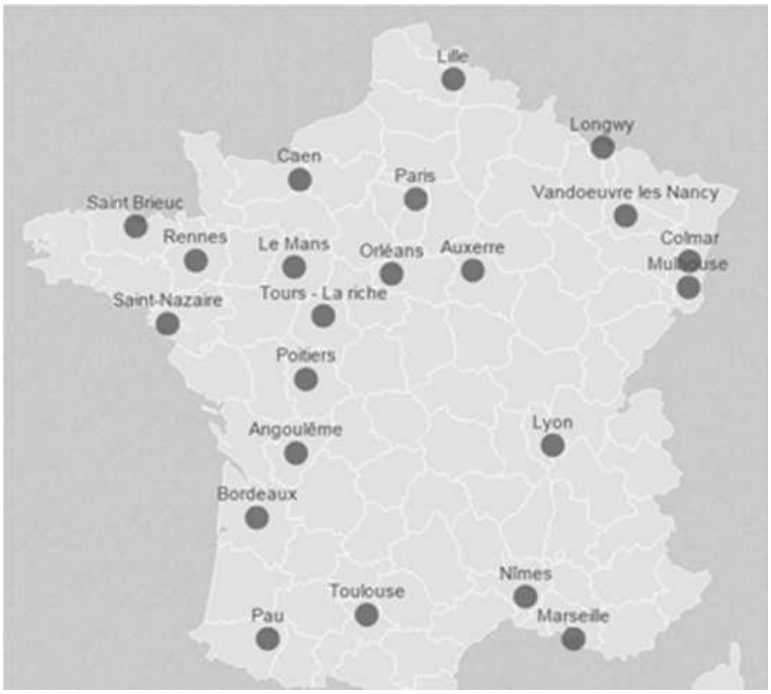


Figure 12. Geographical location of CONSTANCES recruitment centers in France

Randomly selected eligible persons, who agree to participate in the study, receive self-administered questionnaires to complete at home and receive invitation to present to their HSC, where they sign an informed consent and benefit from a health examination.

- **Inclusion of participants**

To obtain a representative sample of the target population and to minimize the biases associated with selection effects at inclusion and during follow-up in CONSTANCES, the following steps were taken **(Zins *et al*. 2015, Goldberg *et al.* 2017)**.

- The sampling base at inclusion is composed of all persons aged 18–69 years and covered by CNAMTS in the catchment areas of the CONSTANCES HSCs.
- Sampling is done within the CNAV (National Retirement Insurance Fund; Caisse Nationale d'Assurance Vieillesse) database, which includes exhaustively all the persons

in France affiliated to the CNAMTS.

- The random drawing is stratified according to unequal inclusion probabilities, based on data from participation in previous surveys involving invitations to HSCs.
- To take into account selection effects due the voluntary participation, a 'control cohort' was drawn from a random sample of 400 000 non-participants, that is, persons who were invited but did not participate, for whom social and occupational, health and healthcare usage data from the same administrative databases as for the participants were prospectively collected.

Figure 13 illustrates the process from sending the letter of invitation to agreeing on the participation in CONSTANCES.

Of note that auxiliary data extracted from CNAV and SNIIRAM cover three years before inception for both the participants and the sample of non-participants. Thus, it is possible to estimate the probabilities of participation in CONSTANCES associated with sociodemographic and health variables using logistic regression models, to compute weights for correcting unit nonresponse and to estimate adjusted prevalence of questionnaire variables. This use of auxiliary data from administrative databases proved to effectively correct for nonresponse **(Santin *et al.* 2014).**

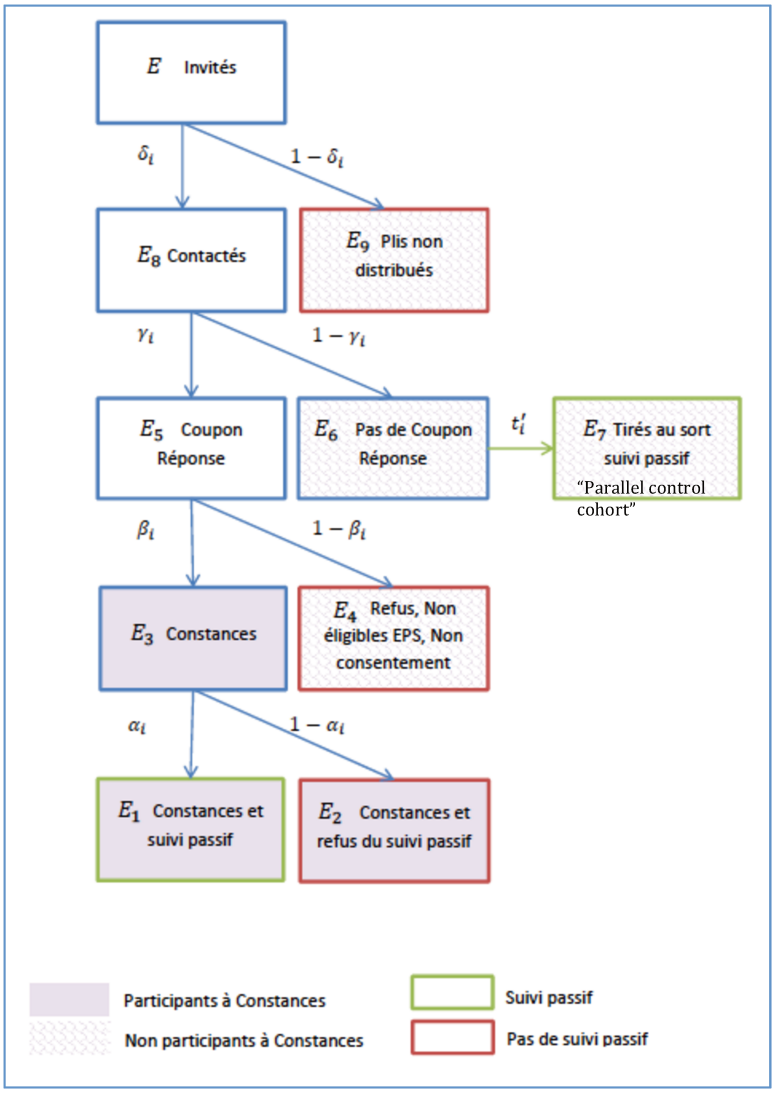


Figure 13. From sending the letter of invitation to participation in CONSTANCES

- **Follow up of participants**

Participants are followed-up through ‘‘active’’ and “passive” procedures **(Zins *et al*. 2015)**. The active procedure involves the participants directly, by completing an annual self-administered questionnaire at home, using either a paper or web-based questionnaire.
They are also invited every 5 years for a new health examination in a HSC.
On the other hand, participants are followed up ‘‘passively’’ (so-called because this follow-up does not require the subjects’ participation) by annual linkage with three national social and health data databases.

1) CNAV database
    a. Collects social and occupational data from different insurance and social organisms by regularly receiving
        i. Annual reports (occupation, salary),
        ii. Information about periods of employment and unemployment e.g., sick leave, maternity leave, unemployment, and diverse social benefits.
2) SNIIRAM database: national healthcare claims system database (Système National d'Informations Inter Régimes de l'Assurance Maladie)
    a. Contains exhaustive individual medical detailed data from different sources
        i. Reimbursement data (doctors and other health professionals visits, prescribed drugs, medical devices)
        ii. So-called ‘‘long-term diseases’’ (serious chronic diseases exempt from co-payments and user fees)
        iii. Hospital discharge records, including for each hospitalization principal and associated diagnoses, medical and technical procedures.
3) National Death Registry-CepiDc
    a. Provides vital status and causes of death

A general overview of the design is illustrated in **Figure 14**

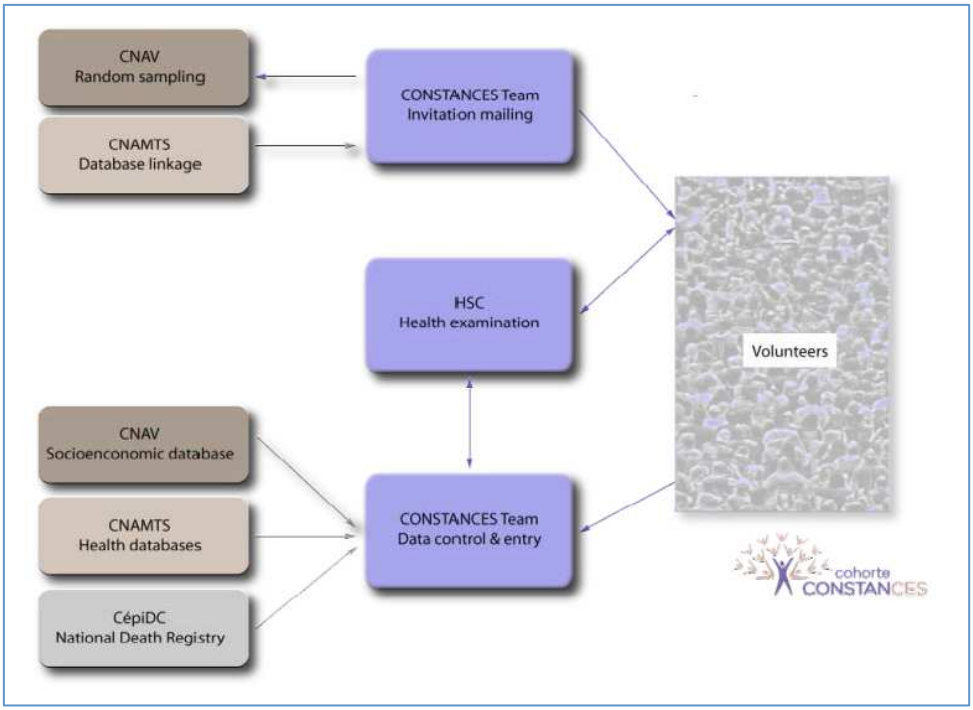


Figure 14. General description of CONSTANCES design

- **Sample size calculation**

Due to its general-purpose objectives, the size of the cohort was not defined by classical power calculations. However, it clear that to be able to answer the many questions raised in varied domains, CONSTANCES must be based on a large sample. Keeping this in mind, as well as costs and different practical constraints for the HSCs, which are basically funded by CNAMTS for delivering free extensive clinical screening for persons affiliated to its health insurance and their dependents, the optimal size decided upon is somehow arbitrary and is 200,000. Details concerning sample size calculation and study power are found at http://www.constances.fr/assets/pdf/calculs_de_puissance.pdf

In fact, in order to assess the potential of CONSTANCES in terms of its capacity to conduct epidemiologic studies likely to have good statistical power, they estimated the number of major health outcomes (deaths and incidence of cancer, ischemic heart disease, and Alzheimer disease) expected at the end of 5, 10, and 15 years of follow-up in a 200,000 persons cohort with an age and sex structure identical to that of the French general population aged 18 to 69 years. Thus, for frequent diseases, numerous studies are possible with satisfactory power, and reliable descriptive data can be produced. Further information regarding the sampling plan and weighting calculations is also found at http://www.constances.fr/assets/pdf/echantillonage_ponderations.pdf

- **Data access**

The CONSTANCES Cohort project is intended to be a centralized infrastructure, under the scientific and technical responsibility of the *Population-Based Epidemiological Cohorts Unit*-UMS 011 (UMS 011), who is experienced in developing and managing large population-based cohorts. The French legal authorities approved all confidentiality, safety and security procedures.

In order to apply for a nested project within CONSTANCES and to access its database, a research proposal should be submitted to the primary investigator of CONSTANCES. After approval by the governing bodies of CONSTANCES: the Steering Committee, the International Scientific Committee and the INSERM Ethics Committee, access to database is granted. The material needed for applying can be downloaded from the CONSTANCES website (http://www.constances.fr/index_EN.php#propose).

As such, in the context of this thesis, we submitted an application to Prof. Marie ZINS to conduct an independent "nested" research project entitled: Hypertension Associated Risk Factors and Implications (HEART) in January 2017, then in June 2017 we received feedback form the scientific committee and after responding to the reviewers, final approval from the concerned committees was received in August 2017. After that, access to the data was possible in September 2017. The main objectives of the research proposal are shown in the table below with some of which are in the context of the thesis.

Table 11. Objectives and corresponding study design of the different analyses conducted as part of the CONSTANCES nested project HEART

Study	Objective	Study Design
1	Prevalence, treatment, control of hypertension and related complications	Cross sectional
2	Determinants of hypertension and predictors of poorly controlled BP	Cross sectional
3	Association between HTN or BP and known non-communicable diseases risk factors	Cross sectional
4	The study the quantitative extent to which the recommended lifestyle factors were determinants of BP level in order to promote their individual or general implementation.	Cross sectional
5	5 year incidence of hypertension and associated health risk factors	Prospective
6	5 year treatment compliance, blood pressure control and development of Cardiovascular diseases	Prospective

II.b Selection of study participants

We requested access to all the participants of CONSTANCES. Between February 2012 and January 2018, a total of 87,808 volunteer participants were recruited and linked to the French health insurance administrative database. We were granted access to the data of all of these participants.

- **Selection of study participants based on analysis' objective**

An illustration of the participants selected based on the study analysis is shown in **Figure 15.**

1. For evaluating the association between unhealthy behavior and hypertension, all individuals from the CONSTANCES database were included except 1,360 individuals with a low BMI, that is, those who are underweight (BMI< 18 kg/m2) and therefore 86,448 individuals were analyzed. Associations were investigated while comparing those with and without hypertension (Article 2).

   The 2018 European guidelines on hypertension, states that "an optimal BMI is unclear but maintenance of a healthy body weight (BMI of approximately 20 - 25 kg/m2) is recommended for non-hypertensive individuals to prevent hypertension, and for hypertensive patients to reduce BP" **(Williams *et al.* 2018)**. As such, people who are underweight might also be exhibiting an unhealthy behavior. In order to simplify the analysis and to reduce bias introduced by a very low BMI, we decided to exclude underweight individuals. This way, focus is on overweight and obesity (as in the recommendations of the European and American guidelines).
2. For examining the association between unhealthy behavior and uncontrolled hypertension, patients known to have hypertension and receiving treatment for their high blood pressure were selected. In other words, hypertensive treated individuals were selected. The reason for choosing treated patients is because the absence of treatment is the reason for their uncontrolled hypertension, therefore they were excluded to have a better estimate for the association between unhealthy behavior and uncontrolled hypertension, uninfluenced by the absence of medication. Similarly to above we also excluded individuals with low BMI (BMI< 18 kg/m2). Thus, from a total of 87,808participants, 10,764 subjects were eligible to be included, of which 54 with low body mass index (BMI <18kg/m2) were excluded. Therefore 10,710 hypertensive treated participants were analyzed (Article 3).

3. For assessing the determinants of uncontrolled hypertension, particularly socio-demographic, clinical and behavioral predictors, hypertensive treated individuals were selected. Similarly to above, the fact they are not receiving treatment is the reason of uncontrolled hypertension; therefore in order to reduce bias introduced by receiving or not BP-lowering medication, hypertensive treated individuals were only selected. There were no exclusion criteria (Article 4).

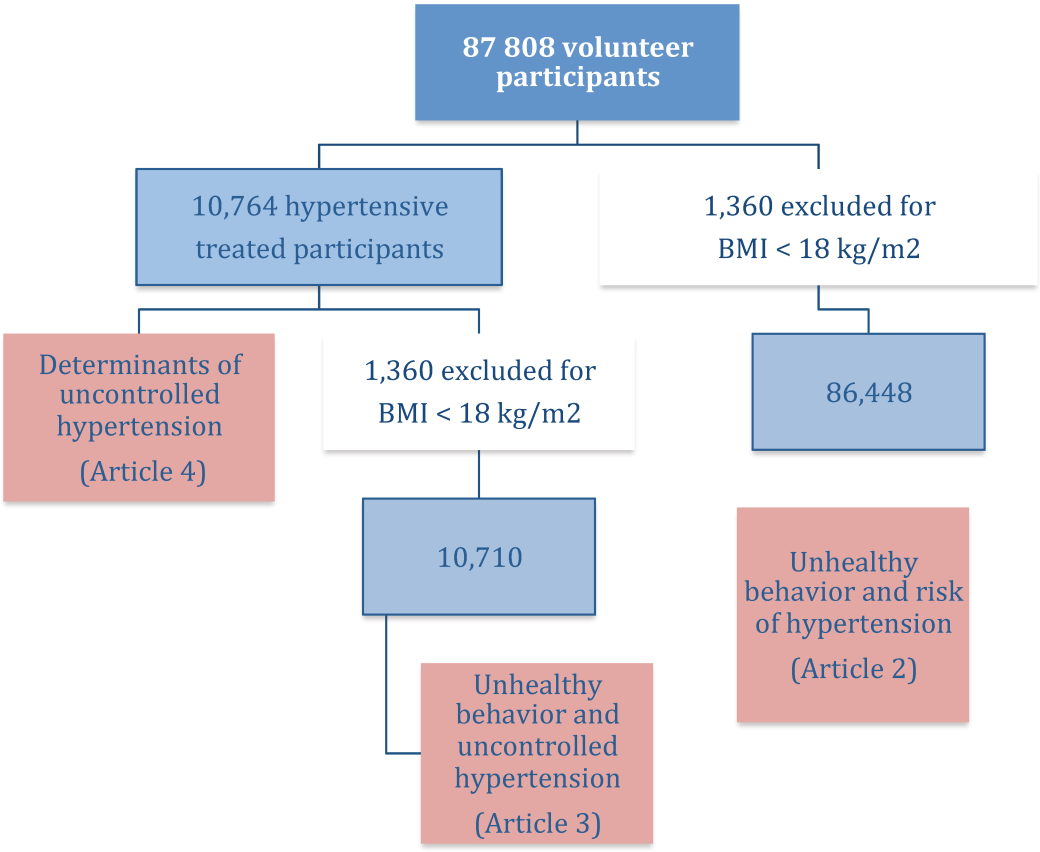


Figure 15. Selection of study participants according to the objective of the analysis
Study subjects of article 2: all participants comparing those with and without hypertension
Study subjects of article 3 and 4: participants with hypertension and receiving anti-hypertensive treatment

The Anatomical Therapeutic Chemical (ATC) classification was used to select anti-hypertensive and BP lowering drugs and included:

- Various antihypertensives: Sartan (ATC codes starting with C09C and C09D; Converting enzyme inhibitor (ATC codes starting with C09A, C09B + C10BX04 code); Other RAAS blockers (ATC class C09X and C09DX02); Thiazide diuretics (ATC codes C02LA01, C03AA01 through C03AA03, C03BA04 through BA11, C03BX03, C03EA through

C03EA04, C07B, C07BA02, C07BB, C07BB02 through C07BB52, C07CA03, C07DA06, C09BA01 through C09BA15, C09DA01 through C09DA08, C09DX01, C09XA52); Loop diuretics: furosemide, bumetanide, piretanide (ATC codes starting with C03C + code C03EB01), Aldosterone antagonists: spironolactone, potassium cancronate, eplerenone, amiloride, and thiazide or furosemide combination (ATC codes starting with C03D or C03E and C07DA06); Beta-blocker (ATC codes beginning with C07); Calcium channel blocker (ATC codes C07FB02 and C07FB03, codes beginning with C08, C09BB, C09DB and C10BX0); other antihypertensive drug: ATC codes starting with C02 excluding indoramine indicated in migraine (code C02CA02).

- Also alpha-blockers used for urological purposes (ATC codes starting with G04CA).

II.c Source and type of data collected

Data was collected from different sources with the detailed list of data available in a catalog that can be downloaded from CONSTANCES' website at www.constances.fr. The overall type of data retrieved from each source can be summarized accordingly:

1) Questionnaires http://www.constances.fr/questionnaires.php
    a. Socio-demographic
    b. Self-reported medical history/Family history
    c. Lifestyle behavior characteristics
2) Medical examination and visit to HSC
    a. Signed informed consent
    b. Medical exam
    c. Paraclinic exam
    d. Anthropometric measurement
    e. Biologic tests
    f. Physician administered questionnaires
        i. Health data; medical history
3) National social and health databases
    a. Occupational status
    b. Health events
    c. Medical acts
    d. Hospitalizations
    e. Medications
    f. ATC classification

Going further in details, **Table 12** summarizes the main type of data collected for each participant from different sources. Of note that the CONSTANCES team provides also some pre-calculated scores (indicateurs disponibles), with a manual describing the calculation and provision of these variables. Examples include:

- Score CES-D AQ_CESD_Score_i for depression
- Smoking status upon inclusion AQ_COMPORT_TcStatut_i for smoking status
- Packs-year AQ_COMPORT_TcPA_i for those who reported as ever smokers
- Score AUDIT AQ_COMPORT_AlcScoreAudit_i for alcohol use identification test

Table 12. Main data regularly collected for each cohort participant in CONSTANCES

DATA	SOURCES
***Social and demographic characteristics*:** Social position, educational and income level, employment and marital status, geographic origin, household composition, socioeconomic status of parents and spouse, and material living conditions (type of housing, household income and wealth, etc.), including geocoding of successive residency addresses.	Questionnaire; CNAV
***Health*:** Personal and family history: cancer, cardiovascular, psychiatric; self-reported health scales: perceived health, quality of life (SF-12 [SF-36 Org]), mental health (CES-D, GHQ-12), and specific scales for cardiovascular, musculoskeletal, and respiratory diseases; incident and prevalent diseases: from self-reports, social security long-term diseases and hospital discharge (ICD-10 codes); sick leaves, handicaps, limitations, disabilities and injuries and healthcare utilization and management (visits to professionals, drugs and other prescriptions); date and cause of death; HSC examination: weight, height, waist-hip ratio, blood pressure, electrocardiogram, visual acuity, hearing, and lung function, laboratory tests (blood sugar level, lipid work-up, liver function tests, blood creatinine levels, complete blood cell counts, urine tests).	Questionnaire; CNAV; HSC; CépiDc
***Lifestyle*:** Smoking and alcohol consumption (past and present), dietary habits and physical activity, marijuana use, sexual orientation.	Questionnaire
***Occupational factors*:** Job history; current job title and employment status; lifelong and current occupational exposure to chemical, physical, and biological agents; postural, mechanical and organizational constraints; stress at work (job content questionnaire-JCQ, effort-reward imbalance-ERI scales)	Questionnaire; MATGENE JEMs
***Physical and cognitive functioning (45 years and older)*:** Evaluation of functional capacities: IADL (Instrumental Activities of Daily Living) scale, ability to use new technologies, and CASP (Control, Autonomy, Self-realization and Pleasure, a quality of life scale particularly appropriate for senior citizens); work-up of tests in HSCs.	Questionnaire; HSC

HSC: HSC health examination; CNAV: CNAV socio-professional database; CNAMTS: SNIIRAM health database; MAGENE: InVS Job-exposure matrices; CépiDc: National Death Register
Data highlighted is the one of particular interest and is needed to answer the objectives of the project HEART and are in the context of the thesis.

Of importance in the process of data collection is the standardization of data collected in the study centers. A quality program was developed for this purpose, including quality assurance and quality control procedures in order to obtain high quality medical examination data. Standard Operating Procedures (SOP) were developed by working groups composed of: personnel from participating sites (Medical Doctors and nurses), epidemiologists and quality assurance specialists and experts of each domain concerned by the data measured or collected **(Zins *et al.* 2015)**. The SOP detail the measurement method for each type of data. The SOPs also describe the material admissible for the study, the required annual certification, the periodic verifications or maintenance (all SOPs can be downloaded from the CONSTANCES website: http://www.constances.fr/espacescientifique/pos.php). For each measurement, all steps of the realization were detailed in order to minimize the inter-operator variation. This ensures appropriate and accurate measurement approaches as well as the successful replication of data collection for all volunteers regardless of when, where and by whom they are performed **(Ruiz *et al.* 2016)**. The SOP for BP measurement will be described below.

II.d Blood pressure measurements and definitions

- **BP measurement**

BP measurements were taken during the clinical examination at the HSC based on standardized operational procedures found at http://www.constances.fr/assets/pdf/pos_pressionarterielle.pdf. Special attention is given to the preparation phase: the size of the cuff should be adapted to the circumference of the arm, one of 3 available commercial sizes are used (children, adults, large) and it should be positioned on the arm at the level of the heart. SBP and DBP were measured in each arm at 2 min interval after 5 min of rest and using an automated oscillometric sphygmomanometer (OMRON® 705 CP- II or OMRON® 705IT provided by the CONSTANCES team). The arm giving the highest SBP was considered the reference arm and a third BP measure was taken after 1 min of rest, the average of these two measurements was considered. A fourth measure was taken on the reference for diabetics and those older than 65 after one minute from a sitting to a standing position, for search of orthostatic hypotension. The chronogram of BP measurements is shown in **Figure 16**

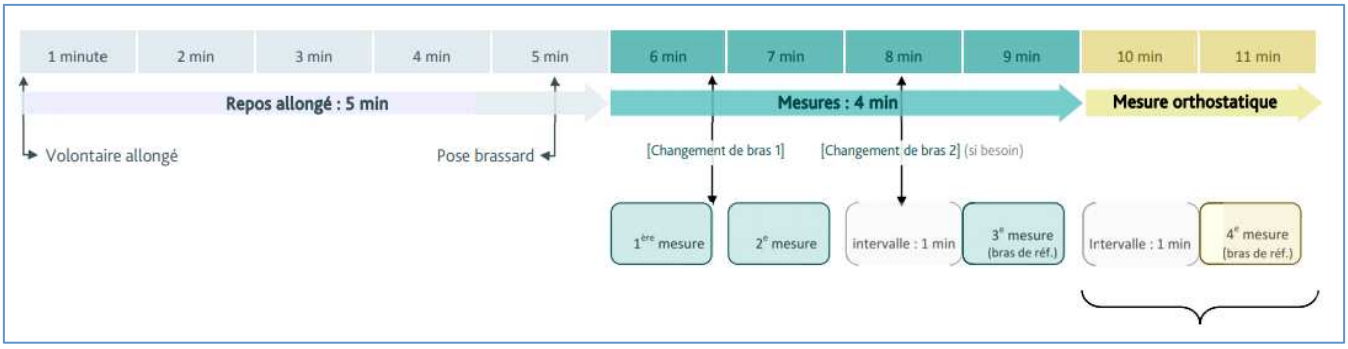


Figure 16. Chronogram of blood pressure measurement according to standard operational procedures

- **Definitions**

Prevalent hypertension

Prevalent HTN was defined according to the 2018 European guidelines **(Williams *et al.* 2018)** by a SBP at least 140mmHg and/or a DBP at least 90mmHg or by individuals taking antihypertensive medications. Similarly to the Lebanese cohort, several items were taken into consideration for the definition of prevalent HTN:

1. Do you have hypertension: documented by the physician on the medical questionnaire administered by the physician during the visit to the HSC (yes/no) and if yes age of diagnosis)
2. Are you receiving treatment for hypertension: documented from insurance record and detected
    a. Through ATC classification for anti-hypertensive and BP lowering drugs explained previously in the section "selection of patients"
3. SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg

Figure 17 illustrate the algorithm followed for determining cases of prevalent hypertension (used for Article 2). It is also briefly described below based on the different possible scenarios:

1) When physicians were documenting the presence of a declared history of hypertension by answering "yes" to the question participant has hypertension. The following scenarios could take place:
    a. Participants **not** taking blood pressure lowering drugs when matched with medication data and their average SBP or DBP did **not** meet the above definition. These participants were **not** considered to be hypertensive.

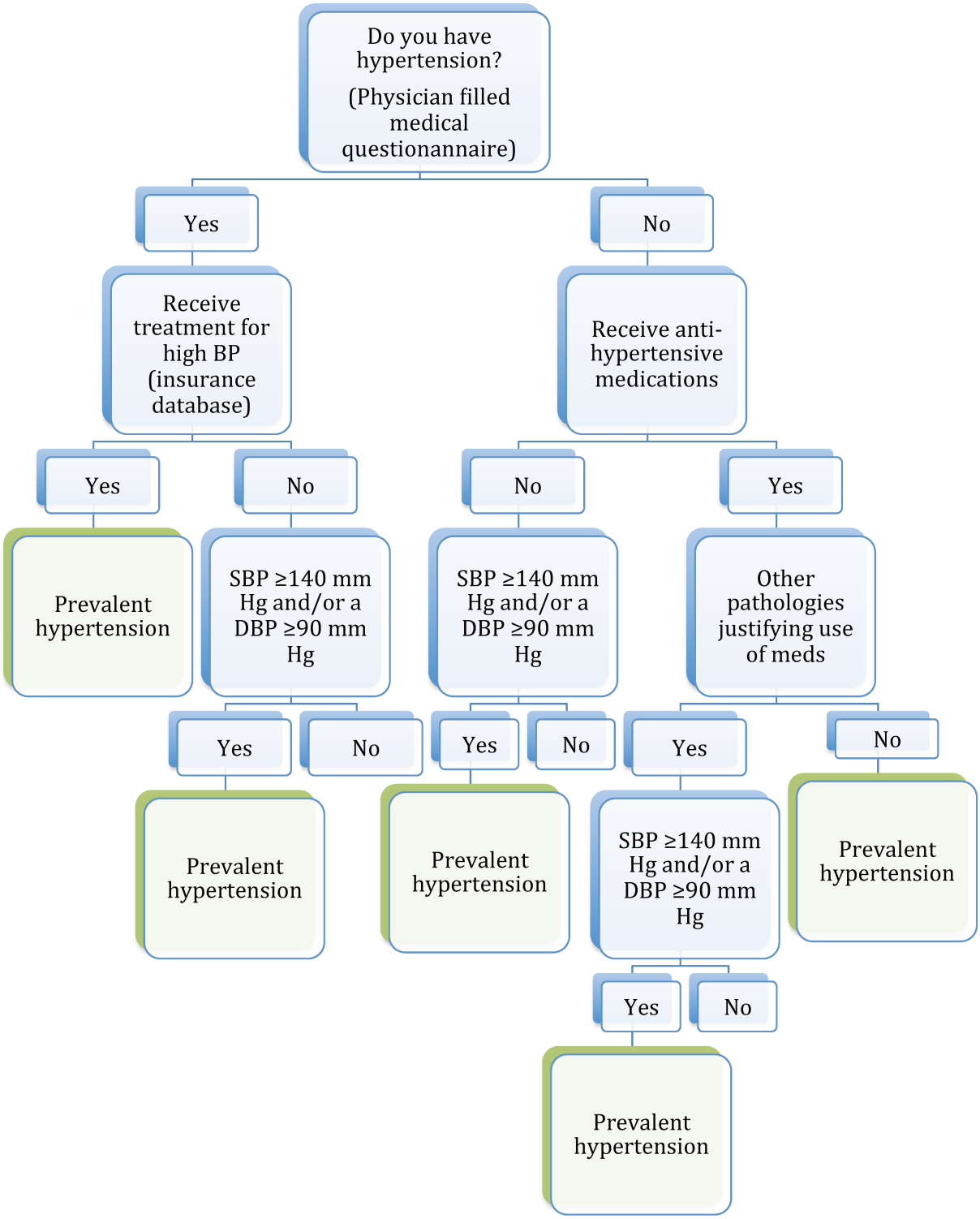
b. Participants **not** taking blood pressure lowering drugs when matched with medication data BUT they had a mean SBP ≥140 mmHg and/or a DBP ≥90 mmHg. These participants were considered to be hypertensive.
c. Participants taking blood pressure lowering medications when matched with insurance data. These participants were considered to have hypertension regardless of their SBP and DBP.

2) When physicians were marking not having a declared history of hypertension by answering "no" to the question, the following scenarios could take place
   a. Participants not receiving a BP lowering medication BUT having a mean SBP ≥140 mmHg and/or a DBP ≥90 mmHg were considered to have prevalent hypertension.
   b. Participants receiving a BP lowering medication BUT for another pathology justifying the use of the medications were not considered having hypertension UNLESS their mean SBP was ≥140 mmHg and/or the DBP was ≥90 mmHg. In other terms those who had a BP <140/90mmHg while using anti-hypertensive medication for another known pathology, were not considered to have hypertension.
   c. Participants receiving a BP lowering medication AND had no known other pathology that can justify the use of these medications, were considered to have prevalent hypertension

Note: The different pathologies justifying the use of anti-hypertensive medications are presented below.

- Pathologies justifying the use of beta-blockers: myocardial infarction, angina, heart failure, cardiac rhythm disorders, migraine, glaucoma, cirrhosis (portal hypertension, prevention of varicose veins rupture), and hyperthyroidism.
- Pathologies justifying the use of ACE inhibitors: Congestive heart failure, myocardial infarction, and renal insufficiency.
- Pathologies justifying the use of CCBs: myocardial infarction and cardiac arrhythmias
- Pathologies justifying the use of diuretics: Cardiac failure and renal insufficiency,
- Pathologies justifying the use of ARB: myocardial infarction, cardiac insufficiency and renal insufficiency

Figure 17. Algorithm for defining prevalent hypertension in CONSTANCE analyses

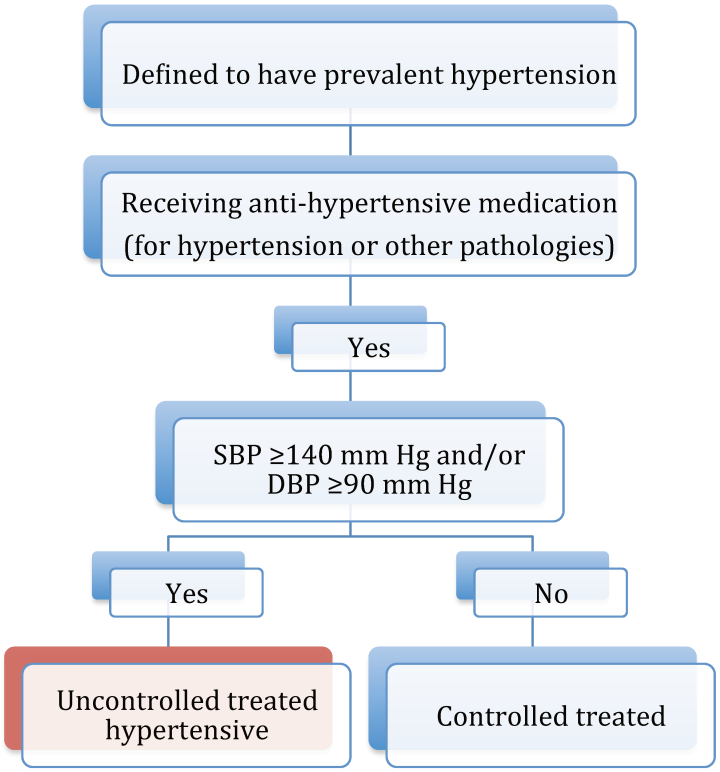


Uncontrolled hypertension

Regardless of study population, uncontrolled hypertension was defined based on the 2018 ESC/ESH Guidelines for the management of arterial hypertension **(Williams *et al.* 2018)** and was determined in selected participants having a mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg.

Articles 3 and 4 are conducted on hypertensive treated individuals to determine association between risk factors and uncontrolled hypertension. As such, uncontrolled hypertension in treated individuals can be summarized as: Having SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg in individuals receiving anti-hypertensive medications, whether for hypertension or other pathologies. On the other hand, controlled hypertension was considered for those controlled on treatment; that is receiving anti-hypertensive medication and their BP is <140/90 mmHg. **Figure 18** illustrates the algorithm for defining BP control in treated individuals.

Figure 18. Algorithm for defining blood pressure control in CONSTANCES analyses



II.e Socio-demographic characteristics

The socio-demographic characteristics of interest were employment, income, marital status and education. They were collected from the different questionnaires used and from the CNAV. They were defined and categorized accordingly:

- Occupational status
    - Was collected according to the French "Occupations and Socioоccupational Categories" [Professions et Categories Socioprofessionnelles] classification system (https://www.insee.fr/en/metadonnees/definition/c1493).
    - Categorized in three broad classes:
      Low: e.g., farmer, blue-collar worker, craftsman, cleaners
      Medium: e.g., clerks, commercial employee, childcare worker, nurse, school teacher, technician, service agent
      High: e.g., manager, engineer, doctor
- Education level
    - Was collected according to the International Standard Classification of Education (ISCED) **(Schneider 2013)**
    - Classified into three levels:
      High school diploma or less (≤ 13 years of education)
      Undergraduate degree (14–16 years of education)
      Postgraduate degree (≥17 years of education)
- Marital status
    - Was categorized into living in couple or single (including widowed or separated/divorced).
- Household monthly income
    - Took into consideration the income provided by individuals in the household
    - Was categorized into: < 1000; 1000-2099; 2100-4199; ≥ 4200 euros per month

II.f Anthropometric measurements and lab tests

Anthropometric measurements obtained during physical examination at the HSC included weight, height and waist-hip ratio. Standard operational procedures exist for each of these measurements.

1. Weight and height were measured respectively with a scale and a measuring rod in light clothes (underwear) and bare feet. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters and was categorized into three classes (similarly to the Lebanese cohort):
   Normal weight (BMI <25 kg/m2)
   Overweight (BMI 25 kg/m2<30 kg/m2)
   Obese (BMI ≥30 kg/m2)
2. Hip circumference was measured using a meter ribbon positioned well horizontally through the widest circumference at the trochanterian level. Waist circumference was measured with a meter ribbon on the skin horizontally on the midaxillary line considered as the marker, midway between the upper edge of the iliac crest and the lower edge of the last palpated costal margin. Cut offs of > 102 cm for men and > 88 cm for female associated with abdominal obesity **(Williams *et al.* 2018)**. Then, waist-hip ratio was calculated.

Laboratory tests were obtained using fasting blood samples and included creatinine, blood glucose, triglycerides, and total and HDL cholesterol. Low-density lipoprotein (LDL) was calculated using the formula: LDL= Total cholesterol – HDL – (triglyceride/2.2).

II.g Medical history and health data

Disease definition and variables of interest were defined using levels from the above obtained laboratory tests, from self-reported health data and from medical databases. We chose these variables based on the literature review and contemporary studies, evaluating risk factors associated with hypertension. As such, the following conditions were defined:

1. Diabetes mellitus status was based on either self-reported type II diabetes, receiving anti-diabetic medication or a fasting blood glucose concentration greater than or equal to 7mmol/L **(Stern *et al.* 2002)**.
2. Hypercholesterolemia was considered if it was recorded by the health care practitioner at the HSC or if total-cholesterol level >6.61 mmol/L (225 mg/dL).

Similarly for hypertriglyceridemia, but if triglyceride levels were >1.7 mmol/L (150 mg/dL). Dyslipidemia was considered if any of hypercholesterolemia, hypertriglyceridemia, LDL >3.0 mmol/L (115mg/dl) or HDL <1.0 mmol/L (40mg/dl) was present **(Williams *et al.* 2018)**.

3. History of CVD was considered as any self-reported previous diagnosis of angina pectoris, MI, CVA or peripheral artery disease.
4. The estimated 10-year risk of coronary heart disease (CHD) was based on the Framingham risk function equation calibrated to the French population **(Empana *et al.* 2011)** and was calculated as 1-(0.97832exp(c)) where c = 6.53∗(log(age) - mean(log(age))) + 15.04∗(sex - prevalence(sex)) - 3.28∗(sex∗log(age) - mean(sex∗log(age))) + 0.51∗(smoking status – prevalence (smoking status)) + 1.03∗(diabetes status - prevalence(diabetes status)) + 1.87* (log(SBP) - mean(log(SBP))) + 2.02*(log(total cholesterol) - mean(log(total cholesterol))) - 1.21∗(log(HDL cholesterol) - mean(log(HDL cholesterol))), with sex = 1 for men and 0 for women and smoking status=1 for current smokers and 0 for non-current smokers. The output of this equation is an estimate of cumulative 10-year risk expressed as a percentage.
5. Chronic kidney disease was defined as known proteinuria or hematuria or decreased renal function (creatinine clearance<60ml/min calculated by the Cockroft-Gault equation) for more than 3 months, or a chronic kidney disease diagnosed by biopsy or renal ultrasound and confirmed by a nephrologist **(Kidney Disease: Improving Global Outcomes Update Work Group 2017)**.
6. As mentioned before, the ATC classification was used to select anti-hypertensive and BP lowering drugs and then they were categorized according to:
    a. Mono-therapy: receiving one antihypertensive agent (one chemical name).
    b. Dual therapy: receiving 2 anti-hypertensive agents
    c. Triple therapy or more: receiving a combination of 3, 4 or more anti-hypertensive agents.

Note: Attention was given to single pill combinations that include two or three chemical agents. Those were considered dual or triple therapy, respectively.

II.h Lifestyle behavior characteristics

Lifestyle behavior was assessed using self-reported questionnaires that gathered information regarding: physical activity, alcohol consumption, nutrition and smoking status. In addition, psychological status was evaluated. The questionnaire entitled "health and lifestyle behavior questionnaire" is found at http://www.constances.fr/medias/base-documentaire/2018/1518026086-questionnaire-mode-de-vie-et-sante.pdf. In order to answer the objectives of the thesis in evaluating the association between unhealthy behavior and hypertension or BP control, unhealthy behavior was defined accordingly.

II.h.1 Physical activity

Physical activity (PA) was assessed taking into consideration PA at work and outside of work.

- PA at work was evaluated for participants who currently work or had worked in the past, excluding those who had never worked. Subjects were asked to evaluate what kind of physical effort they usually did in their current job for current workers or in their last job for past workers.
    - **A physical activity score at work was created that ranges from 1-3:**
    - 1 point for "sedentary", 2 for "moderately active" and 3 for "highly active" subjects.
- PA outside work was assessed through three questions using a 2-points scale fro each one. The first question assessed regular movement by walking or biking and a score of 0 was assigned for answering "no", 1 for "yes, less than 15 minutes per trip" 2 for "yes, 15 minutes or more per trip". The second and third questions assessed sports (running, football, tennis…) and leisure activities (gardening, cleaning house…) respectively; for each question, 2 points were given for answering "Yes, 2 hours or more/week", 1 point for "Yes, less than 2 hours /week" and 0 point for "No".
    - **A physical activity score outside of work was summed from 0-6**
    - PA level was classified as sedentary (0-2), moderately active (3-4) and highly active (5-6)
    - This is the score that was most commonly used later in the analyses.
- For analyses considering PA at work and outside of work, a score was creating considering the following points:
    - PA at work score of 1-3

- PA outside of work score that ranged from 0-6 was transformed into another variable with a another score created that ranged from 1-3:
    - 1 point assigned for sedentary (0-2), 2 for moderately active (3-4) and 3 for highly active (5-6)
- Accordingly a unique physical activity variable accounting for physical activity at work (1-3) and outside work (1-3) was computed, adding the two indicators detailed above and classifying subjects according to 3 PA levels
    - Sedentary (score 2), Moderately active (score 3) and highly active (score 4-6)

Notes:

- The cut points used for categorization of PA levels of the different scores of PA and especially the PA score outside of work was somehow arbitrary, referring to other studies conducted using the database CONSTANCES **(Merle *et al.* 2018)**.
- While computing the above PA scores, the metabolic equivalent for the type of reported physical activity was not calculated. Therefore PA was assessed using a score that is less reproducible than using MET of activities, which could have yielded different results. This limits an adequate comparison of PA levels with other studies, but will be interesting enough to determine the association of PA assessed unconventionally with hypertension.

II.h.2 Alcohol consumption

Chronic alcohol consumption, heavy episodic drinking and alcohol use disorder risk were separately assessed since different measures of alcohol use can have different effect on hypertension and BP. Data on alcohol consumption were collected at enrolment with a validated self-administered questionnaire.

Chronic alcohol consumption and alcohol use disorder risk score were variables computed by the CONSTANCES team and made readily available (indicateurs disponibles). A detailed explanation of how theses variables were computed is available in the manual, but will be briefly explained below.

Chronic alcohol consumption was determined by the following question "How often do you usually drink alcoholic beverages?" and possible answers ranged from 1) never, 2) once a month or less, 3) 2-3 times per month and 4) once or more a week. Those who reported

drinking alcohol at least once per week were asked to report all the alcoholic beverages (quantity and type of drinks) consumed the previous week as seen in **Figure 19.**

118. *Pouvez-vous décrire votre consommation de boissons alcoolisées standard au cours de* ***la dernière semaine ?***

ℹ Si vous **n'avez pas consommé de boisson alcoolisée les jours indiqués,** cochez « Aucune boisson alcoolisée ».

	Aucune boisson alcoolisée	Bière, cidre	Vin, Champagne	Alcool fort	Apéritif	Premix*	Cocktail
			Rouge, blanc, rosé	Whisky, Vodka, Pastis, etc.	Suze, Martini, etc.		Gin tonic, Punch, Téquila sunrise, etc.
		Nb de verres standard	Nb de verres standard	Nb de verres standard	Nb de verres standard	Nb de bouteilles 30 cl	Nb de verres standard
Du Lundi au Jeudi (Nombre de verres par jour en moyenne)	☐ 1						
Vendredi	☐ 1						
Samedi	☐ 1						
Dimanche	☐ 1						

*Premix : petite bouteille de 30 cl contenant un mélange d'alcool et de soda d'environ 5° : Smirnoff Ice™, Boomerang™, etc.

Figure 19. Type and amount of alcoholic beverages consumed each day in the previous week from the CONSTANCES questionnaire

Then the amount of alcohol found in the type of alcoholic beverage consumed and the quantity consumed was considered according to below **Figure 20**, consequently the amount in grams of weekly alcohol intake was calculated.

Figure 20. Amount of alcohol based on standard type of alcoholic beverage from the CONSTANCES questionnaire

Chronic alcohol consumption was subsequently categorized into 3 levels based on the WHO classification, considering gender-specific alcohol recommendations **(WHO, International Guide for Monitoring Alcohol Consumption and Related Harm, 2000)**. **Table 13** presents the definition of alcohol consumption levels in men and women, which was used in the different analyses.

Table 13. Categorization of alcohol consumption in men and women

	Men	Women
Never/light	0–3 glass/week (0–30 g/week)	0–2 glass/week (0–20 g/week)
Moderate	4–21 glass/week (40–210 g/week)	3–14 glass/week (30–140 g/week)
Heavy	>21 glass/week (>210 g/week)	>14 glass/week (>140 g/week)

Heavy episodic drinking frequency was measured as a categorical variable based on the answer to the following question: "How often do you drink six or more standard alcoholic beverages on the same occasion?" Participants had to choose among five responses: 1) Never; 2) Less than once per month; 3) Every month; 4) Every week; and 5) Every day or almost. Categories 2) and 3) were aggregated, as well as categories 4) and 5), in order to compute a categorical variable with 3 categories as follows: 1) Never, 2) At most once a month and 3) More than once a month.

Alcohol use risk was also studied and categories were defined based to the French version of the Alcohol Use Disorders Identification Test (AUDIT) **(Gache *et al.* 2005)**. The AUDIT was developed in 1989 by the World Health Organization (WHO) and has been updated in 1992 to match the DSM-IV criteria for alcohol abuse and dependence. It consists of a 10-item self-administered questionnaire built as a transcultural screening tool about recent alcohol use, alcohol dependence symptoms and alcohol-related problems. The AUDIT score ranges from 0 to 40 and alcohol use disorder severity is classified according to recommended AUDIT risk levels **(Babor *et al.* 2001)**, which are:

- No abuse or dependence (Score ≤7 for men and ≤6 for women)
- Abuse (Score > 7 and ≤ 12 for men; and > 6 and ≤11 for women)
- Dependence (Score >12 for men and > 11 for women)
- Missing score: for those who completed less than 4 items of the 10 items that constitute the score.

II.h.3 Nutrition and dietary assessment

Dietary assessment was done through a validated 52-items food frequency questionnaire (FFQ) indicating the frequency of intake of different food types and beverages. The possible answers were: never or rarely, less than once per week, almost once per week, 2 or 3 times per week, 4 to 6 times per week, once per day (in this case indicate how many times per week). From the FFQ we were able to assess adherence to dietary recommendations using 2 scores:

1) The modified National Program on Nutrition and Health – Guideline Score (mPNNS-GS) **(Estaquio *et al.* 2009)**. This score evaluates adherence to French dietary guidelines established by the National Program on Nutrition and Health (Programme National Nutrition Sante; PNNS).
2) Dietary Approach to Stop Hypertension score (DASH)

In general the higher the scores the better the adherence to dietary recommendations, indicating overall better dietary pattern habits or dietary quality **(Fung *et al.* 2008)**. Both scores were studied, evaluating the effect of dietary compliance on hypertension. However since the mPNNS is less commonly used in the literature and is specific toward French recommendations, the DASH score was the one adopted in most analyses and in the analyses of the published papers.

1) Computation of the mPNNS score:

As mentioned, based on adherence to French dietary guidelines established by the National Program on Nutrition and Health (Programme National Nutrition Sante; PNNS), the modified PNNS guideline score (mPNNS-GS) was created **(Estaquio *et al.* 2009)**. A detailed explanation of the score computation is found in **Appendix 3.1**. Briefly, it is a 13.5 points score calculated on the basis of 12 dietary components: 8 components refer to French food serving recommendations and 4 concern nutrients and food groups whose consumption is to be limited. A score of 0, 0.5, 1, 1.5 or 2 can be assigned to the components based on recommended frequency consumption, -0.5 can be given for over consumption of salt and sugar. In addition, a penalty (deduction from the score) is given to individuals whose energy intake exceeds the estimated energy need by more than 5%, by the same fraction of energy exceeded. The energy needs were estimated on the basis of basal metabolic rate calculated according to Schofield and physical activity level **(Schofield 1985)**. Therefore, the mPNNS-GS is the sum of the 12 component scores minus the penalty points; for example, an energy

over-consumption of 10% would result in reducing a mPNNS-GS of 7 points to 6.3 points. The score was then categorized into 3 levels indicating dietary adherence to French recommendations:

- Low adherence when mPNNS-GS score <5.5
- Medium adherence when the score is between 5.5 to <8
- High adherence when the score is ≥8

2) Computation of the DASH score:

The DASH score was constructed based on food groups described by Fung and colleagues **(Fung *et al.* 2008)** and a detailed explanation is found in **Appendix 3.2**. Briefly, the score considers 8 food and nutrients for which consumption is emphasized or minimized in the DASH diet. For each food group, consumption was divided into quintiles, and participants' intakes were assigned 1-5 points according to a gender-specific intake ranking **(Karanja *et al.* 1999, Fung *et al.* 2008)**. Dietary components for which consumption should be increased (fruits, vegetables, nuts and legumes, low-fat dairy, whole grains) were rated on a scale of 1–5; the higher the score, the more frequent the consumption of that food. Dietary constituents for whom low consumption is desired (sodium, sweetened beverages, red and processed meats), were scored on a reverse scale, with lower consumption receiving higher scores. Component scores were summed, and an overall DASH score ranging from 8-40 was calculated. Overall DASH score was subsequently collapsed to tertiles for analysis; higher tertile indicating a higher dietary quality and dietary adherence, yielding 3 categories: low, medium and high. Of note that the cut points used in dividing the score into tertiles were different according to study population and gender; they were obtained form the statistical software used.

II.h.4 Smoking status

Data regarding smoking was gathered through the self-reported "health and lifestyle habit" questionnaire. Questions gathered history of smoking any form of tobacco (cigarette, cigarillo, pipe, cigar), as well as electronic cigarettes and cannabis. Smoking tobacco was the main form considered in the analyses. Three variables with regards to smoking were readily available from the CONSTANCES team (indicateurs disponibles) to assure uniformity of definitions among ancillary projects; the variables were:

- Smoking status during life: Non-smokers or smokers/ex-smokers
- Smoking status upon inclusion: Non-smokers or smokers or ex-smokers
- Pack-years: calculated for those who ever smoked. For each type of tobacco product (cigarette, cigarillo, pipe, cigar) multiply the average number smoked by the corresponding duration of smoking (number of years) then divide by the number of cigarettes / cigarillos ... contained in a package.

The global smoking status during life was the variable mostly used in the different analyses of this thesis.

II.h.5 Unhealthy behavior definition

Lifestyle behavior changes recommended through worldwide guidelines for the prevention and management of hypertension adopt a multidisciplinary healthy approach that includes adhering to DASH style diet, reducing salt intake, limiting alcohol consumption, increasing physical activity and reducing weight while achieving normal BMI **(Williams *et al.* 2018, Whelton *et al.* 2018)**. As such, and in the context of this thesis answering the objectives aiming to evaluate the magnitude of the individual and combined effect of unhealthy behavior on hypertension and BP control, unhealthy behavior was defined accordingly:

- Sedentary level physical activity
- Heavy alcohol consumption
- Low/medium adherence to dietary recommendations (either mPNNS or DASH)
- Overweight/obese

Accordingly, participants could exhibit 0 (none), 1, 2, 3, or 4 unhealthy behaviors. The 3 or 4 unhealthy behavior groups were aggregated to ensure adequate sample size. But, the "none" group was considered separately even if the sample size was small and used as a reference to other groups. Thus, unhealthy behavior was categorized as none, 1, 2 or ≥3.

II.h.6 Depressive symptoms

Lastly, regarding evaluating psychological distress and hypertension, depressive symptoms (mood or moral) were assessed using the validated self-administered Center of Epidemiologic Studies Depression scale (CES-D) **(Fuhrer & Rouillon 1989)**, which is found in the "health and lifestyle behavior" questionnaire available at http://www.constances.fr/medias/base-documentaire/2018/1518026086-questionnaire-mode-de-vie-et-sante.pdf. The CES-D scale is a 20-item questionnaire that evaluates the

frequency of depressive symptoms during the previous week and designed for use in population-based epidemiologic studies. For negatively worded items such as "I felt depressed", "I felt lonely", "Everything I did was an effort" a score of 0 was assigned for rarely or never, 1 for some or little of the time, 2 for occasional or moderate, 3 for most or all the time. For positively worded items such as "I felt happy" an inverse score was assigned. Scores range from 0 to 60, with high scores indicating greater depressive symptoms **(Morin *et al.* 2011)**. Similarly to other variables, the CES-D score was readily available by the CONSTANCES team (indicateurs disponibles). The score was later divided into dichotomous variable suing a cut-point level of 16, yielding the following categories:

- Non-depressive: score <16
- Depressive: score ≥16

III. Statistical analysis

- **Questionnaires review**

Particularly for the Lebanese cohort, the questionnaires were reviewed and double-checked for consistency, accuracy and clearness by two independent observers; an additional audit was performed on a randomized 5% of the collected data sheets.

- **Hypertension adjusted prevalence rate**

Although we calculate a crude prevalence rate of hypertension in the Lebanese cohort, but to adjust for the Lebanese population, the prevalence rate of hypertension was age, sex- and dwelling region adjusted based on the figures published by the Lebanese Ministry of Social Affairs and the Central Administration of Statistics **(Central Administration of Statistics, Ministry of Social Affairs, 2016)**. Cluster effect was taken into account, according to the method described by Rumeau-Rouquette et al. **(Rumeau-Rouquette *et al.* 1985)**.

- **Descriptive statistics**

In all the analyses, initially descriptive analysis was performed. Participants' characteristics were presented using counts and percentages for categorical variables or mean ± standard deviation to describe normally distributed quantitative variables and medians with interquartile ranges to describe non-normally distributed variables

- **Association measures**

Bivariate analysis was carried out to compare characteristics in men and women. It was also used in a sex-stratified approach to measure the association of the different characteristics between the following study population groups:

- In individuals with or without hypertension,
- In those with controlled or uncontrolled hypertension
- In those with 0, 1, 2, or 3 unhealthy behavior

Here, the association between the different unhealthy behaviors and particular variables of interest such as the dietary components of the LMDS, with hypertension was evaluated.

Relationship between categorical variables whether dichotomous or multinomial qualitative variables were examined using Pearson's Chi^2 or Fisher's exact tests when normal or abnormal distribution was assumed, respectively. Comparison of continuous

quantitative variables was analyzed using student (independent) T-test and Mann-Whitney test when applicable. Similarly, for dependent groups, the paired sample student t-test or Wilconxon Signed Rank test were used when appropriate. Moreover, for differences among the means of three or more independent groups, the ANOVA test and the Kruskall Wallis test were used, respectively, when appropriate. Lastly, the Crude associations between quantitative variables (SBP, dietary scores) will be studied using Pearson's correlation coefficient. Overall, unadjusted odds ratio (OR) were calculated along with 95% CI.

- **Multivariable analysis models**

Logistic regression

Logistic regression was used for several analyses. In order to provide association measures adjusted to age and gender (or stratified by sex) logistic regression was used to compare characteristics between the different study groups described above, including comparing characteristics of subjects according to the number of unhealthy behaviors. In addition, to evaluate independent predictors of hypertension (article 1) or uncontrolled hypertension (article 4), age-adjusted multivariate analysis was performed using a backward stepwise likelihood ratio logistic regression for the whole sample and for each gender. The potential predictive factors were those with $p<0.2$ obtained fro the bivariate analysis and included: socioeconomic characteristics, lifestyle factors including nutritional and psychological variables and known cardiovascular risk factors. The HosmereLemeshow goodness-of-fit test was used to assess the overall fit of the model, and adjusted odds ratios (ORa) were calculated.

Also with logistic models, the association between prevalent hypertension (article 2) or uncontrolled hypertension (article 3) and unhealthy behaviors was estimated. In both analyses we used same models: In a first step, models were adjusted for age, education and monthly income (Model 1). In a second step, models were further adjusted for diabetes and hypercholesterolemia (Model 2). At first, separate models for each unhealthy behavior using categorical variables and binary variables were performed. Then, the association between hypertension and the number of unhealthy behaviors (0-≥3) independently associated with hypertension was evaluated. In the case of article 3 the association studied was with uncontrolled hypertension. Adjusted odds ratios (ORa) were presented along with 95% confidence interval (CI).

Linear regression

Multivariable linear regression models that are conducted in an age adjusted and gender stratified approach, were used to assess the association between BP parameters and risk factors of interest. Regression coefficients (β) and their 95% CIs will be presented. Moreover, the adjusted coefficient of determination, *R2*, and the squared partial correlation coefficient, *r2*, which are used to describe the contribution to BP variability for each parameter, will be reported for each model. Homoscedasticity, normality of the residuals and multicollinearity will be assessed.

General linear model

The General Linear Model is used to study unadjusted and adjusted mean BP parameters across the different categories of selected variables (such as BMI categories, alcohol consumption level, physical activity level, dietary assessment (LMDS, mPNNS or DASH) and BDS-22 quartiles score). Among other factors, the model was adjusted for age, gender and the use of blood pressure lowering medications (articles 1 and 4).

- **Statistical software and significance**

Analyses on the Lebanese cohort were done using Statistical Package for Social Sciences, SPSS version 21·0 (IBM Corporation, Armonk, NY, USA). While analyses on CONSTACNES, were performed with Statistical Analysis System, SAS 9.4 (SAS Institute, Cary, North Carolina, USA). In all analyses, valid 2-sided p-values were reported and $p \leq 0.05$ was considered significant.

CHAPTER 4:
RESULTS AND DISCUSSION

Publications: Abstracts and Articles

Article 1 (Published)

Title: Prevalence and Risk Factors of Hypertension: a Nationwide Cross-Sectional Study in Lebanon

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Abstract:

Background: The prevalence of hypertension is reaching epidemic proportions globally. Lifestyle modifications are recommended in worldwide guidelines to help in its prevention and control. However, data in Lebanon is limited.

Objectives: Therefore, we aim to determine the lifestyle and socioeconomic determinants of hypertension and to evaluate the influence of dietary and psychological factors on blood pressure.

Methods: Cross-sectional analyses were conducted using a multistage cluster sample across Lebanon. Information on lifestyle behaviors were collected using validated questionnaires. Dietary adherence and psychological distress were assessed computing the Lebanese Mediterranean diet score and the Beirut distress score respectively. Blood

pressure measurements were taken following standardized protocol. Participant's characteristics were compared and stratified by sex. Gender specific age-adjusted multivariable analyses were performed using logistic regression models and general linear models.

Results: A total of 2014 participants were included. The prevalence and control rates of hypertension were 31.2% and 28.7% respectively. In both sexes, the prevalence increased with increasing age, higher body mass index and history of cardiovascular diseases (adjusted odds ratio (OR_a) >1.0, p<0.01 for all). In women, there was an association between hypertension and educational level (OR_a 0.513; 95% confidence interval (CI), 0.289-0.885), physical activity (OR_a 0.478; 95% CI 0.273-0.837) and having diabetes (OR_a 2.427; p=0.002). In men marital status (p=0.039) and alcohol consumption (p=0.014) were associated with hypertension. In both gender, systolic BP was significantly higher in overweight and obese participants (p≤0.001). Adherence to the Lebanese Mediterranean diet was associated with a lower SBP in women only. There was no relationship with SBP and psychological distress in both sexes (p>0.05 for both).

Conclusion: Body mass index persisted as the main contributory modifiable factor of hypertension in men and women. Accordingly, prevention of HTN at the population level should focus mainly on overweight prevention.

Keywords: Hypertension, blood pressure, Mediterranean diet, epidemiology, body mass index, lifestyle behavior

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ORIGINAL PAPER

WILEY

Prevalence and risk factors of hypertension: A nationwide cross-sectional study in Lebanon

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There is limited epidemiologic data on hypertension (HTN) in Lebanon. This study aimed to determine the prevalence and associated risk factors of HTN in the adult Lebanese population and evaluate the association between dietary and psychological factors on systolic blood pressure (SBP). Cross-sectional analyses were conducted using a multistage cluster sample across Lebanon. A total of 2014 participants were included. The prevalence and control rates of HTN were 31.2% and 28.7%, respectively. In women, educational level and physical activity were negatively associated with HTN ($P < .05$ for both) and adherence to the Lebanese Mediterranean diet was associated with a lower SBP. Other factors were associated with HTN in men. There was no relationship with SBP and psychological distress. Of the modifiable risk factors, body mass index persisted as the only contributory factor in both sexes ($P < .01$). Accordingly, prevention of HTN at the population level should focus mainly on overweight prevention.

1 | INTRODUCTION

Hypertension (HTN) was found to be the number 1 risk factor in 2010 for the Global Burden of Disease study and contributes to the burden of heart disease, stroke, kidney failure, dementia, premature death, and disability.[1,2] Over the years, the prevalence of HTN reached epidemic proportions, affecting over one-quarter of the worldwide adult population, causing an estimated 10 million deaths every year.[2] Furthermore, national health surveys in various countries have shown a high prevalence of poor blood pressure (BP) control at the 140/90 mm Hg threshold among hypertensive patients. In the United States, more than 45% did not have their BP controlled,[3] and in Europe, BP control ranged between 40% and 19%.[4] In the Middle East and Arab countries, existing studies reported a higher rate of uncontrolled BP, ranging from 56% (Tunisia) to 92% (Egypt and Syria).[5] Although the pathogenesis of primary HTN is still not completely understood, mixing obvious genetic and environmental factors, the increasing prevalence is attributed to population growth, aging, and behavioral risk factors.[6] Several clinical trials studied the efficacy of lifestyle modifications to reduce BP, leading to the commonly known 5 non-pharmacologic recommendations in worldwide guidelines on the prevention and management of hypertension:[7] (1) maintain a normal body weight (body mass index [BMI] < 25 kg/m^2), (2) engage in regular aerobic physical activity, (3) limit alcohol consumption to 2 drinks a day for men and 1 drink a day for women; (4) reduce dietary salt intake to no more than 6 g/day; and (5) adopt a dietary approach to stop hypertension (DASH), including consuming a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. More recently, nutrition and dietary patterns have been an area of research focus, such as the French Nutrition and Health Program that aimed at the prevention of high BP through nutrition.[8] Lebanon is an upper-middle-income country with a surface area of 10 542 Km^2 and a population of 4.42 million (year 2012).[9] Limited epidemiologic data on HTN exist in Lebanon. In fact, one previous study reported that the prevalence of HTN and BP control were 35.9% and 27%, respectively.[10] However, the study had several limitations: (1) the study population was not representative of the Lebanese population, (2) it did not extensively discuss the risk factors associated with HTN, and (3) it did not address the relationship between HTN and lifestyle behaviors, including dietary habits. Therefore, we conducted this study to determine the prevalence and risk factors of hypertension specifically in the Lebanese adult population. We aimed to evaluate the association between HTN and lifestyle behaviors as well as to explore the relationship between the Lebanese-adopted Mediterranean diet and psychological factors on the systolic BP.

2 | METHODS

2.1 | Study design and study population

In the framework of the study, assessing the prevalence of cardiovascular diseases (CVD) and their risk factors among Lebanese residents using a multistage cluster sample all over Lebanon,[11] we conducted this ancillary cross-sectional analysis. Using a software program, we randomly selected 100 circumscriptions from the list of circumscriptions in Lebanon (villages, towns, and cities)[12] without excluding any territory. Residents older than 20 years (arbitrary decision) with no a priori exclusion criteria were then randomly selected from the list of dwellers provided by the local authority. Participants were interviewed at a governmental location and data were gathered after giving oral and written consent. The sample size consisted of a total of 2088 participants,[11] of which 40 were excluded for missing the majority of the data, 23 for missing blood pressure values, and 11 for using vasoactive medications. Accordingly, 2014 participants were included in the current analysis.

2.2 | Anthropometrics and blood pressure measurements

Anthropometrics and BP measurements were taken using a standardized protocol. Using an automatic validated device, systolic BP (SBP) and diastolic BP (DBP) were measured twice at 1-minute intervals in a seated position after 5 minutes of rest.[13] The average of the 2 measurements was used for the analyses. Pulse pressure (PP = SBP – DBP) and mean arterial pressure (MAP = 2/3 * DPB + 1/3 * SBP) were calculated according to the usual formula. Random capillary blood glucose (RCBG) was measured using Accu-Check® Performa.[14] Weight measurement was performed with an electronic scale with participants wearing light clothes; height was measured with a wall-mounted measuring rod. BMI was calculated and reported as a continuous variable and divided into 3 categories: normal weight (BMI < 25 kg/m^2), overweight (BMI 25 kg/m^2 < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Waist circumference was measured in cm.

2.3 | HTN prevalence and BP control definitions

Prevalent HTN was defined by an SBP ≥ 140 mm Hg and/or a DBP ≥ 90 mm Hg or by individuals who were currently taking antihypertensive medications.[7] Participants who reported being hypertensive, but who were not taking blood pressure lowering drugs and their average SBP or DBP did not meet the above definition, were not considered to be hypertensive. Uncontrolled BP was defined as mean SBP ≥ 140 mm Hg and/or mean DBP ≥ 90 mm Hg.[7]

2.4 | Chronic diseases variables definitions

Diabetes was defined as random capillary blood glucose (RCBG) >200 mg/dL or self-reported medication use for glucose control.[15] Hypercholesterolemia or hypertriglyceridemia was considered when participants reported having a blood test that diagnosed the condition or if they were taking lipid-lowering medications. We defined coronary heart disease (CHD) as any self-reported history of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or angina using the "definite angina" definition of the Rose Angina Questionnaire.[16] Participants who self-reported a

history of stroke or transient ischemic attack were identified as having cerebrovascular accident (CVA), even if non-medically validated. We computed the variable (any cardiovascular disease [any CVD]) as those with either CHD or CVA. A family history of premature CVD was defined as a fatal or non-fatal CVD event or/and established diagnosis of CVD in a first-degree relative (father, mother, brother, sister, children) younger than 55 years for males and 65 years for females.[17]

2.5 | Mediterranean diet and psychological distress score calculation

Dietary habits were assessed using the Lebanese Mediterranean Diet Score (LMDS). Details concerning the questionnaire and the choice of the detrimental and beneficial components have been explained elsewhere.[18] Briefly, an adapted nonquantitative food frequency questionnaire (FFQ) was used. For components presumed to be beneficial (raw vegetables, cooked vegetables, fruits, olive oil, food grains and beans, fish, rice and pasta, whole grain bread, and white bread), a score of 0 was assigned for people who did not consume it at all; a score of 1 was assigned for those who consumed it less than 2 times a week; a score of 2 for those who consumed it 3 to 6 times per week; a score of 3 for those who consumed it at least once per day; and a score of 4 for those who consumed it at every meal. For components presumed to be health detrimental (meat, fried food, sweets, and fast food), an inverse score was assigned. Thus, the LMDS score ranged from 0 to 52 (maximal adherence).

We assessed psychological distress using the Beirut Distress Scale (BDS-22), a scale that was developed and validated in the Lebanese population. The BDS-22 consisted of 22 items and had a 4-point (0 to 3) Liker-type response format. Thus, the BDS-22 ranged from 0 to 66 (maximum psychological distress).[19]

2.6 | Behavioral risk factors definitions

Leisure time physical activity was assessed based on the updated Compendium of Physical Activities. The type and frequency of exercise were self-reported. For each activity, we assigned the corresponding metabolic equivalent (MET) value, then a 3-level classification was done as follows: light-intensity (1.6 to 2.9 METs), moderate-intensity (3 to 5.9 METs), and vigorous-intensity (≥6 METs) activities.[20] Insufficient physical activity was defined as <150 minutes of light- or moderate-intensity exercise/week and <75 minutes of vigorous-intensity exercise/week.[21] Current smokers were defined as individuals who smoked a cigarette and/or a water pipe in the previous 12 months and those who had quit within the past year. Participants who had quit more than a year earlier were considered former smokers.[22] For those who previously smoked, cumulative dosing of cigarettes was calculated as the average number of daily packs multiplied by the corresponding duration of smoking (pack × years), while that of water pipe was calculated as the mean number of weekly water pipes multiplied by the duration of smoking (water pipe × years).[23]

2.7 | Statistical analysis

The questionnaires were reviewed and double checked for consistency, accuracy, and clearness by two independent observers; an additional audit was performed on a randomized 5% of the collected data sheets. To adjust for the Lebanese population, the prevalence rate of hypertension was age, sex, and dwelling region (adjusted based on the figures published by the Lebanese Ministry of Social Affairs and the Central Administration of Statistics).[24] Cluster effect was taken into account, according to the method described by Rumeau-Rouquette et al[25] Initially, descriptive analysis was performed using counts and percentages or mean ± standard deviation (SD). Bivariate analysis was then carried out to compare the variables in men and women and in individuals with and without hypertension, stratified by sex. For categorical variables, we used the Pearson's Chi-squared or Fisher's exact tests when applicable. Continuous quantitative variables were analyzed using student (independent) *T*-test and Mann-Whitney test when normal or abnormal distribution was assumed, respectively. Age-adjusted odds ratios (ORa) were calculated along with 95% confidence interval (CI). Multivariable analysis was performed using a backward stepwise likelihood ratio logistic regression for the whole sample and for each gender; ORa were presented. In addition to age and area of residence, the independent factors included, socioeconomic status (SES) characteristics (marital status, education, income, working status), lifestyle factors (BMI, physical activity, alcohol consumption, smoking, and dietary status using the LMDS), psychological factors using the BDS-22, and known cardiovascular risk factors (diabetes, history of CVD). Using the General Linear Model, unadjusted and adjusted mean systolic BP were studied across the different categories of selected variables (such as BMI categories, LMDS and BDS quartiles score); the model was adjusted for age and the use of BP-lowering medications. Valid 2-sided *P*-values were reported, $P < .05$ was considered statistically significant. All analyses were done using SPSS, version 21.0.

3 | RESULTS

3.1 | Baseline characteristics and prevalence of HTN

The baseline characteristics and BP parameters of the study population are summarized in Tables 1 and 2, respectively. The prevalence of HTN was 31.2% (95% CI, 29.2% to 33.3%). The prevalence, treatment, and control of HTN are described in Figure 1; among the 628 individuals with hypertension, 255 (40.5%) were not treated, while 374 (59.5%) reported current use of BP-lowering medications. Of the treated participants, 180 (48.2%) had their BP under control, however, this accounts for an overall 28.7% control rate when all hypertensive patients were considered. Men were more likely to have hypertension and an uncontrolled BP compared to women (*P* value for both <.001).

Among treated individuals, the mean ± SD number was 1.6 ± 0.7 medications; 183 (57.0%) were taking monotherapy, 102 (31.8%) bitherapy, and 34 (11.2%) 3 or 4 drugs. Table 2 presents the agents used

TABLE 1 Baseline characteristics of the study population

Characteristic	All	Men	Women
Number	2014	976 (48.5%)	1038 (51.5%)
Age (y)	41.3 (17.0) [20-97]	41.1 (16.8) [20-93]	41.5 (17.1) [20-97]
BMI (Kg/m^2)	26.8 (4.9) [14.7-66.6]	27.6 (4.6) [14.7-45.0]	26.1 (5.2) [16.0-66.6]
Waist circumference (cm)	92.4 (17.1) [32-198]	97.3 (15.3) [39-198]	87.7 (17.4) [32-198]
Working status			
No	681 (33.9)	150 (15.4)	531 (51.2)
Yes	1239 (61.6)	755 (77.6)	484 (46.7)
Retired	90 (4.5)	68 (7.0)	22 (2.1)
Marital status			
Single	785 (39.3)	414 (42.5)	371 (36.2)
Married	1085 (54.3)	528 (54.3)	557 (54.3)
Widowed/divorced	129 (6.5)	31 (3.2)	98 (9.6)
Educational level			
Primary-complementary	657 (32.8)	304 (31.3)	353 (34.2)
Secondary	427 (21.3)	210 (22.1)	216 (21.0)
University and higher	917 (45.8)	450 (47.3)	462 (44.8)
Income of the house/mo			
More than 2 000 000 LBP	584 (31.2)	326 (35.9)	258 (26.9)
1 000 000-2 000 000 LBP	512 (27.4)	252 (27.7)	260 (27.1)
500 000-1 000 000 LBP	529 (28.3)	232 (25.5)	297 (31.0)
<500 000 LBP	243 (13.0)	99 (10.9)	144 (15.0)
Region type			
Urban	1007 (52.5)	504 (54.6)	503 (50.6)
Rural	910 (47.5)	419 (45.4)	491 (49.4)
Smoking status			
Never smoker	859 (42.7)	303 (31.0)	556 (53.6)
Current smoker	1006 (50.0)	595 (61.0)	411 (39.6)
Previous smoker	149 (7.4)	78 (8.0)	71 (6.8)
Alcohol consumption			
No consumption	1105 (58.3)	413 (44.8)	692 (71.0)
Occasional	712 (37.6)	436 (47.3)	276 (28.3)
Everyday	79 (4.2%)	73 (7.9)	6 (0.6)
Quantifying the level of PA			
No regular activity	1356 (67.4)	623 (63.8)	733 (70.7)
Light- Moderate intensity (MET ≤6)	409 (20.3)	175 (17.9)	234 (22.6)
Vigorous intensity (MET >6)	248 (12.3)	178 (18.2)	70 (6.8)
Physically active	466 (23.9)	261 (27.9)	205 (20.3)
LMDS	30.9 (4.6) [15-49]	30.5 (4.7) [15-49]	31.4 (4.4) [18-47]
BDS-22	32.6 (11.1) [1-66]	31.3 (10.8) [2-66]	33.8 (11.3) [1-66]

BDS-22, Beirut distress scale; BMI, body mass index (Kg/m^2); LBP, Lebanese pounds; LMDS, Lebanese Mediterranean diet score; MET, metabolic equivalent; PA, physical activity; SD, standard deviation.

Data are mean (SD) [Minimum-Maximum] for quantitative variables or percent for categorical.

TABLE 2 BP parameters and use of anti HTN medications

Characteristic	All	Men	Women	*P* value
Number	2014	976 (48.5%)	1038 (51.5%)	
SBP	120.9 (18.1) [78-220]	125.7 (16.1) [78-220]	116.3 (18.6) [78-205]	<.001
DBP	75.7 (11.4) [50-127]	77.5 (11.1) [50-127]	74.0 (11.3) [50-123.5]	<.001
MAP	90.8 (12.3) [60-144.7]	93.6 (11.5) [65-144.7]	88.1 (12.5) [60-142.8]	<.001
PP	45.2 (13.8) [10-130]	48.3 (13.1) [18-130]	42.3 (13.8) [10-110.5]	<.001
HR	80.2 (13.8) [30-200]	79.9 (13.3) [30-170]	80.6 (14.3) [36-200]	.263
Type of anti-HTN medication	373	182 (48.8)	191 (51.2)	
ACE inhibitor	55 (17.1)	28 (17.8)	27 (16.5)	.745
ARB	107 (33.2)	62 (39.2)	45 (27.4)	.025
Thiazide diuretic[a]	72 (22.4)	32 (20.3)	40 (24.4)	.373
CCB	78 (24.3)	34 (21.7)	44 (26.8)	.280
BB	165 (51.4)	66 (42.0)	99 (60.4)	.001
Diuretics[b]	22 (6.8)	10 (6.3)	12 (7.3)	.725

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, beta blockers; CCB, Calcium channel blocker (including dihydropiridine [DHP] and non-DHP's); DBP, diastolic blood pressure; HTN, hypertension; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
Data are mean (SD) [Minimum-Maximum] for quantitative variables or percent for categorical.
[a]Thiazide diuretic including: hydrochlorothiazide, chlorthalidone and indapamide.
[b]Diuretics including: loop, potassium sparing and aldosterone antagonists.

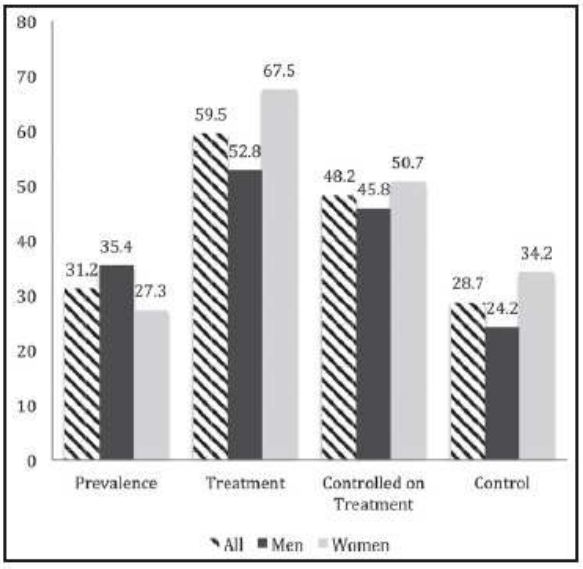

FIGURE 1 Hypertension prevalence, treatment, and control among men and women

(the total percentage is higher than 100 because a patient may be using one or more drug) with beta-blockers as the most commonly used medications (51.4%), followed by angiotensin receptor blockers (33.2%).

3.2 | Nutritional and psychological aspect

Components of the LMDS are presented in Table S1 and were compared in hypertensive and non-hypertensive individuals. Detrimental components, such as fast food, fried food, meat, and sweets were consumed less frequently in hypertensive individuals than in non-hypertensive. This resulted in a higher mean ± SD detrimental score of 13.4 ± 2.6 compared to 12.1 ± 2.7 in non-hypertensive individuals ($P < .001$), suggesting that those with hypertension were more adherent to the LMD. Beneficial components, such as olive oil, white bread, whole grain bread, cooked vegetables, and fruits were consumed more frequently by those with hypertension (P trend for all, $P < .05$). The beneficial score was similar in both groups ($P > .05$; data not tabulated). The overall LMD score is discussed in the gender-stratified analysis.

Age and sex-adjusted multivariable logistic regression of all components of the LMDS found a significant negative relationship with the consumption of olive oil and vegetable intake and a positive association with white bread (all $P < .05$).

Components of the BDS-22 score were compared in both groups. Patients with HTN were more likely to exhibit more distress in 13 of the 22 items such as: feeling more despaired, empty, on the edge, etc. ($P < .05$).

3.3 | Association between risk factors and HTN

Results of the gender-stratified analysis comparing studied factors in hypertension and non-hypertension groups are presented in Tables 3 and 4. Large differences in age between both groups were found and accordingly, age-adjusted ORs are presented along with 95% CI. Overall, HTN was more prevalent in men (ORa = 1.459, 95% CI = 1.207-1.763). In both sexes, HTN was more common with increasing BMI ($P < .001$) and in those with a lower range income than 2 000 000 Lebanese pounds

TABLE 3 Females' characteristics in individuals with and without HTN

Characteristic	Patients with HTN	Patients without HTN	*P* value	Age adjusted OR (95% CI)	*P* value
Number	283 (27.3%)	754 (72.7%)			
Age (y)	57.3 (17.2) [20-97]	35.6 (12.8) [20-89]	*	1.090 (1.078-1.102)	<.001
SBP	135.4 (18.4) [85-205]	109.1 (12.6) [78-139]	*	1.101 (1.084-1.118)	<.001
DBP	83.2 (12.4) [50-123.5]	70.6 (8.6) [50-89]	*	1.136 (1.112-1.161)	<.001
MAP	100.6 (12.3) [66.7-142.8]	83.4 (8.9) [60-103.7]	*	1.165 (1.137-1.194)	<.001
PP	52.2 (17.0) [10-110.5]	38.5 (10.2) [16-80]	*	1.049 (1.034-1.063)	<.001
HR	78.5 (12.5) [44-164]	81.4 (14.8) [36-200]	**	1.005 (0.993-1.016)	.447
Waist circumference (cm)	95.7 (17.7) [36-198]	84.7 (16.3) [32-189]	*	1.017 (1.007-1.027)	<.001
BMI (Kg/m^2)	29.2 (6.0) [16-66.6]	25.0 (4.3) [16-45.1]	*	1.103 (1.066-1.141)	<.001
BMI categories			*		
Normal	67 (24.1)	416 (55.5)		1	<.001
Overweight	100 (36.0)	230 (30.7)		1.513 (1.003-2.281)	.048
Obese	111 (39.9)	104 (13.9)		2.959 (1.913-4.577)	<.001
Working status			*		
No	200 (70.4)	331 (44.0)		1	.008
Yes	68 (23.9)	416 (55.2)		0.568 (0.395-0.816)	.002
Retired	16 (5.6)	6 (0.8)		1.117 (0.405-3.083)	.831
Marital status			*		
Single	50 (17.8)	320 (43.0)		1	.382
Married	172 (61.2)	385 (51.7)		0.988 (0.648-1.509)	
Widowed/divorced	59 (21.0)	39 (5.2)		1.452 (0.761-2.771)	
Educational level			*		
Primary-complementary	171 (61.5)	182 (24.2)		1	.003
Secondary	62 (22.3)	154 (20.5)		0.752 (0.496-1.140)	.179
University and higher	45 (16.2)	417 (55.4)		0.458 (0.293-0.718)	.001
Income of the house/mo in LBP			*		
More than 2 000 000	36 (14.1)	222 (31.5)		1	.001
1 000 000-2 000 000	68 (26.7)	192 (27.3)		2.591 (1.154-5.819)	.021
500 000-1 000 000	78 (30.6)	219 (31.1)		2.830 (1.265-6.329)	.011
<500 000	73 (28.6)	71 (10.1)		4.634 (1.967-10.917)	<0.001
Region type			***		
Urban	122 (45.4)	381 (52.6)		1	
Rural	147 (54.6)	344 (47.4)		1.578 (1.117-2.231)	.010
Smoking status			*		
Never smoker	153 (54.1)	403 (53.4)		1	.724
Current smoker	97 (34.3)	314 (41.6)		0.869 (0.611-1.236)	
Previous smoker	33 (11.7)	38 (5.0)		0.999 (0.531-1.879)	
Cigarette smoking			**		
Non-current smoker[a]	218 (78.4)	601 (82.6)		1	.422
0.1-14.9 cig-pack-years	21 (7.6)	74 (10.2)		0.637 (0.360-1.126)	
15-29.9 cig-pack-years	16 (5.8)	27 (3.7)		0.751 (0.361-1.563)	
≥30 cig-pack-years	23 (8.3)	26 (3.6)		0.888 (0.455-1.733)	

(Continues)

TABLE 3 (Continued)

Characteristic	Patients with HTN	Patients without HTN	*P* value	Age adjusted OR (95% CI)	*P* value
Water pipe smoking			*		
Non-current smoker[a]	245 (90.7)	573 (80.0)		1	.799
0.1-19.9 WP-years	8 (3.0)	65 (9.1)		0.890 (0.396-2.001)	
20-39.9 WP-years	5 (1.9)	36 (5.0)		0.879 (0.277-2.789)	
≥40 WP-years	12 (4.4)	42 (5.9)		1.420 (0.665-3.033)	
Alcohol consumption			NS		
No consumption	194 (73.2)	498 (70.2)		1	.690
Occasional	70 (26.5)	206 (29.1)		0.930 (0.635-1.364)	
Everyday	1 (0.4)	5 (0.7)		0.321 (0.019-5.356)	
Level of PA			*		
No regular activity	220 (77.5)	514 (68.1)		1	.008
Light-moderate (MET ≤6)	62 (21.8)	172 (22.8)		0.678 (0.455-1.009)	.055
Vigorous (MET >6)	2 (0.7)	69 (9.1)		0.127 (0.026-0.619)	.011
Physically active	40 (14.5)	165 (22.4)	**	0.412 (0.261-0.651)	<.001
Random blood sugar	126.1 (48.7) [76-424]	105.8 (26.6) [46-494]	*	1.008 (1.003-1.013)	.002
LMDS	32.0 (4.9) [19-46]	31.2 (4.2) [18-47]	NS	0.978 (0.936-1.023)	.339
BDS-22	35.7 (12.5) [11-66]	33.1 (10.7) [1-66]	**	1.009 (0.994-1.024)	.256
FH of premature CHD	20 (7.2)	77 (10.5)	NS	0.651 (0.362-1.171)	.152
Diabetes	104 (36.7)	53 (7.0)	*	3.451 (2.244-5.307)	<.001
Any CVD	55 (19.4)	33 (4.4)	*	4.077 (2.306-7.208)	<.001
Hypercholesterolemia	109 (38.5)	81 (10.8)	*	2.976 (2.011-4.405)	<.001
Hypertriglyceridemia	62 (22.5)	34 (4.6)	*	3.094 (1.854-5.164)	<.001
Rated health score	6.6 (1.9) [0-10]	7.8 (1.7) [0-10]	*	0.781 (0.707-0.863)	<.001

BDS-22, Beirut Distress Scale; BMI, Body mass index (Kg/m^2); CHD, Coronary heart disease; CVD, Cardiovascular disease (including patients with CHD and cerebrovascular accident); DBP, diastolic blood pressure; HTN, hypertension; LBP, Lebanese pounds; LMDS, Lebanese Mediterranean diet score; MAP, mean arterial pressure; MET, metabolic equivalent; PA, physical activity; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; WP, waterpipe.

Data are mean (SD) [Min-Max] for quantitative variables or percent for categorical. *≤.001, **≤.01, ***≤.05, NS (Non significant) >.05.

[a]Previous smokers were considered non-smokers.

(1333 USD). In females, HTN was more prevalent in those living in a rural area ($P < .01$), while it was less prevalent in working individuals ($P = .01$) and in those with a higher level of education ($P = .001$). In males, HTN was prevalent in married vs single individuals ($P < .05$).

Regarding lifestyle behaviors, in both females and males, HTN was less seen in those with "vigorous intensity" physical activities compared to no activity (P trend <.05) and in women who are physically active versus those who are not (ORa 0.412; $P < .001$).

Among biologic risk factors and in both sexes, HTN was more common in individuals with hypertriglyceridemia and hypercholesterolemia. Previous CVD was also a common predictor of HTN as well as an overall lower self-rated mean ± SD health score. Diabetes was associated with HTN in women.

There was no statistically significant difference with regards to dietary compliance (LMDS) and psychological distress (BDS-22) and the development of HTN (Tables 3 and 4; $P > .05$). However, when evaluating the relationship between LMDS and SBP in a model adjusted to age and use of BP-lowering medication, women had significantly lower adjusted SBP values in the higher quartiles ($P = .003$), suggesting that compliance with the Lebanese Mediterranean diet may be associated with a lower SBP level (Figure 2A), but in men we found an insignificant adjusted lower SBP. There was no relationship between BDS-22 and SBP in both men and women (Figure 2B). Last, SBP significantly increased in both men and women among different and ascending BMI categories (Figure 2C; P for trend <.01).

3.4 | Multivariable analysis

Table 5 presents the results of the multivariable logistic regression analysis that accounts for potential confounding factors. HTN increased with increasing age, BMI, and presence of previous CVD in both men and women, and was higher in married men and in women with diabetes. On the other hand, HTN decreased in men with occasional alcohol consumption and in women with higher education and physical activity.

TABLE 4 Males' characteristics in individuals with and without HTN

Characteristic	Patients with HTN	Patients without HTN	*P* value	Age adjusted OR (95% CI)	*P* value
Number	345 (35.4)	630 (64.6%)			
Age (y)	51.3 (17.7) [20-91]	35.5 (13.4) [20-93]	*	1.064 (1.054-1.074)	<.001
SBP	138.8 (16.4) [86-220]	118.6 (10.4) [78-139]	*	1.133 (1.112-1.154)	<.001
DBP	84.8 (12.4) [50-127]	73.5 (7.9) [50-89.5]	*	1.136 (1.114-1.158)	<.001
MAP	102.8 (11.6) [65-144.7]	88.5 (7.6) [66-105.3]	*	1.185 (1.157-1.214)	<.001
PP	54.0 (16.1) [20-130]	45.1 (9.8) [18-70]	*	1.044 (1.031-1.058)	<.001
HR	79.7 (13.1) [48-156]	80.0 (13.4) [30-170]	NS	1.007 (0.995-1.018)	.240
Waist circumference (cm)	101.5 (16.5) [41-198]	95.0 (14.2) [39-180]	*	1.028 (1.017-1.038)	<.001
BMI (Kg/m^2)	29.0 (5.0) [14.7-45]	26.8 (4.2) [17.3-45]	*	1.118 (1.082-1.156)	<.001
BMI categories			*		
Normal	68 (19.9)	230 (36.6)		1	<.001
Overweight	140 (41.1)	284 (45.2)		1.374 (0.937-2.013)	.103
Obese	133 (39.0)	115 (18.3)		3.793 (2.506-5.740)	<.001
Working status			*		
No	47 (13.6)	103 (16.4)		1	.576
Yes	248 (71.9)	507 (80.7)		0.937 (0.601-1.461)	
Retired	50 (14.5)	18 (2.9)		1.307 (0.619-2.758)	
Marital status			*		
Single	72 (20.9)	342 (54.4)		1	.020
Married	259 (75.3)	269 (42.8)		1.556 (1.062-2.280)	.023
Widowed/divorced	13 (3.8)	18 (2.9)		0.761 (0.314-1.843)	.544
Educational level			*		
Primary-complementary	152 (44.3)	153 (24.4)		1	.582
Secondary	74 (21.6)	137 (21.8)		1.017 (0.678-1.525)	
University and higher	117 (34.1)	338 (53.8)		0.854 (0.593-1.230)	
Income of the house/mo in LBP			**		
More than 2 000 000	96 (29.1)	230 (39.8)		1	.006
1 000 000-2 000 000	109 (33.0)	143 (24.7)		2.200 (1.302-3.716)	.032
500 000-1 000 000	91 (27.6)	140 (24.2)		1.794 (1.052-3.059)	.003
<500 000	34 (10.3)	65 (11.2)		0.950 (0.484-1.863)	.184
Region type			NS		
Urban	171 (51.5)	334 (56.4)		1	.112
Rural	161 (48.5)	258 (43.6)		1.278 (0.944-1.731)	
Smoking status			*		
Never smoker	116 (33.5)	187 (29.6)		1	.108
Current smoker	185 (53.5)	411 (65.1)		0.709 (0.513-0.979)	
Previous smoker	45 (13.0)	33 (5.2)		0.859 (0.473-1.558)	
Cigarette smoking			***		
Non-current smoker[a]	207 (62.7)	372 (63.4)		1	.582
0.1-14.9 cig-pack-years	39 (11.8)	102 (17.4)		0.967 (0.614-1.522)	
15-29.9 cig-pack-years	26 (7.9)	46 (7.8)		0.923 (0.525-1.622)	
≥30 cig-pack-years	58 (17.6)	67 (11.4)		0.732 (0.473-1.135)	

(Continues)

TABLE 4 (Continued)

Characteristic	Patients with HTN	Patients without HTN	*P* value	Age adjusted OR (95% CI)	*P* value
Water pipe smoking			**		
Non-current smoker[a]	273 (83.0)	422 (73.6)		1	.669
0.1-19.9 WP-years	22 (6.7)	77 (13.4)		0.728 (0.427-1.241)	
20-39.9 WP-years	9 (2.7)	18 (3.1)		1.072 (0.449-2.562)	
≥40 WP-years	25 (7.6)	56 (9.8)		1.070 (0.624-1.834)	
Alcohol consumption			*		
No consumption	171 (52.6)	242 (40.5)		1	<.001
Occasional	132 (40.6)	304 (50.9)		0.519 (0.376-0.717)	<.001
Everyday	22 (6.8)	51 (8.5)		0.655 (0.349-1.229)	.187
Level of PA			*		
No regular activity	224 (64.9)	398 (63.2)		1	.001
Light-moderate (MET ≤6)	97 (28.1)	78 (12.4)		1.495 (1.028-2.174)	.035
Vigorous (MET >6)	24 (7.0)	154 (24.4)		0.502 (0.309-0.816)	.005
Physically active	84 (25.1)	177 (29.4)	NS	0.808 (0.575-1.137)	.221
Random blood sugar	125.8 (50.3) [61-583]	115.9 (39.6) [70-369]	**	0.999 (0.996-1.002)	.519
LMDS	31.7 (4.3) [21-43]	29.9 (4.8) [15-49]	*	0.969 (0.932-1.008)	.113
BDS-22	32.1 (10.7) [2-66]	30.9 (10.8) [2-66]	NS	1.009 (0.995-1.023)	.221
FH of premature CHD	35 (10.5)	47 (7.6)	NS	1.548 (0.941-2.548)	.085
Diabetes	97 (28.1)	84 (13.3)	*	1.167 (0.802-1.699)	.420
Any CVD	83 (24.1)	35 (5.5)	*	2.711 (1.692-4.343)	<.001
Hypercholesterolemia	99 (28.7)	55 (8.7)	*	2.027 (1.355-3.031)	.001
Hypertriglyceridemia	74 (22.1)	40 (6.4)	*	2.390 (1.529-3.734)	<.001
Rated health score	7.4 (1.9) [0-10]	8.3 (1.5) [0-10]	*	0.862 (0.786-0.945)	.002

BDS-22, Beirut Distress Scale; BMI, body mass index (Kg/m^2); CHD, coronary heart disease; CVD, cardiovascular disease (including patients with CHD and cerebrovascular accident); DBP, diastolic blood pressure; HTN, hypertension; LBP, Lebanese pounds; LMDS, Lebanese Mediterranean diet score; MAP, mean arterial pressure; MET, metabolic equivalent; PA, physical activity; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; WP, waterpipe. Data are mean (SD) [Min-Max] for quantitative variables or percent for categorical. *≤.001, **≤.01, ***≤.05, NS (Non-significant) >.05.
[a]Previous smokers were considered non-smokers.

4 | DISCUSSION

Our findings show that, in Lebanon, the prevalence of HTN and poor BP control reached epidemic proportions comparable to the highest worldwide percentages. In both sexes, HTN prevalence increased with increasing age and BMI, and in the presence of previous CVD. In addition, in women there was an association between HTN and diabetes, educational level, and physical activity. While in men it was seen with alcohol consumption and marital status.

4.1 | Prevalence and control of HTN

The prevalence and control of HTN were 31.2% and 28.7%, respectively, and were similar to the rates of 35.9% and 27% described from a previous study.[10] A lower prevalence rate can be caused by differences in the study design of both studies. Nevertheless, this little inter-country variation strengthens the accuracy of our results, represents the most up-to-date national data on HTN, and stresses that public health policies should be implemented in Lebanon in an effort to reduce the clinical implications of HTN. Our study was also in accordance with data from Arab countries, where a recent review found that the overall estimated prevalence of HTN was of 29.5% and highlighted a low level of optimal BP control.[5] Despite the fact that worldwide guidelines recommend beta-blockers as first-line in patients with CHD,[7] half of the hypertensive participants received beta-blocker medications while less than one-third had compelling indications for their use. This demonstrates the persistent and extensive use of beta-blockers for the treatment of hypertension.[10]

4.2 | Risk factors of HTN

4.2.1 | BMI

We found that a higher BMI was significantly and positively related to an increase in the prevalence of HTN. This association has been discussed in previous studies with recent prospective data revealing that obesity is linked with incident HTN.[26] Results of our study further ascertain the association between BMI and HTN; BMI persisted as a

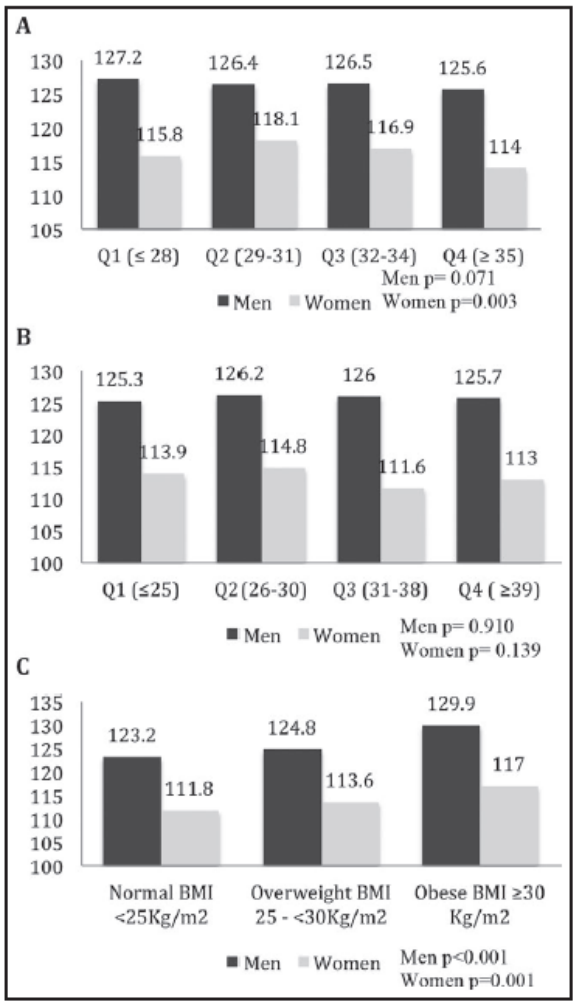

FIGURE 2 Adjusted mean SBP among studied factors (A) Adjusted mean SBP according to dietary adherence by LMDS quartiles. (B) Adjusted mean SBP according to psychological stress by BDS-22 quartiles. (C) Adjusted mean SBP among body mass index categories. BDS-22, Beirut distress score; LMDS, Lebanese Mediterranean diet score; SBP, Systolic blood pressure. Model: adjusted for age and use of anti-hypertensive medications

main causative modifiable factor in the HTN multivariable model in both sexes. Furthermore, an increase in the SBP was seen across BMI categories, underlining the influence of BMI on SBP variability. These findings further suggest that weight management and maintaining a healthy BMI should be emphasized for the primary prevention of HTN and in an effort to improve BP control in treated hypertensives.

4.2.2 | Alcohol consumption

Our study described that HTN decreased with occasional alcohol consumption in men only. Differences between men and women with regards to alcohol intake and the risk of developing hypertension have been seen elsewhere,[27] and can be attributed to the differences in the pattern of drinking and beverage choice. In addition, we believe that alcohol was underreported in our study because of religious reasons, thus further influencing our observed gender difference.

TABLE 5 Multivariable logistic regression analysis: adjusted relationship between HTN and its risk factors

Independent variables in logistic regression model	Exp B	95% CI	P value
Dependent variable is HTN			
In males			
Age, y	1.047	1.033-1.061	<.001
BMI, Kg/m^2	1.118	1.077-1.161	<.001
Occasional alcohol vs none	0.634	0.432-0.849	.014
Married vs single	1.568	1.023-2.405	.039
Previous CVD	3.115	1.750-5.545	<.001
In females			
Age, y	1.073	1.056-1.090	<.001
BMI, Kg/m^2	1.079	1.030-1.131	.001
University or higher education	0.513	0.289-0.885	.018
Physically active	0.478	0.273-0.837	.010
Diabetes	2.427	1.381-4.265	.002
Previous CVD	5.015	2.139-11.759	<.001

BMI, body mass index; CVD, cardiovascular disease.

4.2.3 | Physical activity

We found an inverse association between physical activity (PA) and the prevalence of HTN in women. This protective association has been demonstrated abundantly in studies conducted on women only.[28] Also, this relationship appears to be with vigorous intensity activity compared to a low-to-moderate activity. This association was not seen in men and could be explained by under reported occupational or leisure time PA as well as by differences in socioeconomic and cultural factors that could interfere with being physically active.[29]

4.2.4 | Lebanese Mediterranean diet

Adherence to LMDS was associated with reduced changes in mean levels of SBP across higher quartiles of the LMDS in women only. This relationship was described in a recent meta-analysis of 6 studies, where adopting a MD pattern for at least 1 year had reduced the SBP levels.[30] In addition, discrepancies between sexes was found in the Nutrinet-Sante study, reporting that in women only, adherence to French nutritional guidelines as well as to a MD and the DASH diet was inversely associated with BP levels.[31] Since our results were adjusted to age and use of antihypertensive medications only, other confounding factors such as socioeconomic, BMI, and other behavioral factors may explain the difference found between men

and women. Some data suggest that sex-related characteristics such as the level of sex hormones may interact with the results.[32] Future research is needed to clarify the long-term role of the LMD on BP prevention and management.

4.2.5 | Socioeconomic status factors

Level of education remained significantly and inversely associated with HTN in women only. The advantage of education as a measure of SES is that it can be reliably recalled and unaffected by later adult health. Education level was suggested as the most important SES factor with an impact on HTN,[33] and data from studies conducted in many countries (United States, Jamaica, Korea, Austria) found this association in women only.[34-36] Although the reasons for the gender-related difference remain unclear, individuals with lower education may exhibit unhealthy dietary and lifestyle behaviors (smoking, exercise, and alcohol) as well as less psychological support, increasing the risk of HTN.[35,37] In addition, in Lebanon, cultural and social factors may influence education in women and subsequent employment; those with low education may have higher possibility of unemployment and poor health compared to men.[38] Marital status was associated with hypertension and was observed in married men. This was also seen in a previous study in Lebanon[10] and the gender difference can be attributed to the cultural and social factors mentioned above.

5 | STUDY STRENGTHS AND LIMITATIONS

The main strength of our study was its design, adopting a population-based approach, a nationally representative sample, and a random selection of participants. In addition, we used standardized protocols in the different measurements taken, including BP, as well as validated and well-recognized questionnaires to gather demographic, socioeconomic, and behavioral and health-related factors. We also used the BDS-22, an instrument that proved to adequately correlate with well known and recognized scales, to measure psychological distress.[20] Additionally, the LMD score was correlated with European MD scores and aligned closest to Italians, highlighting that the LMD is in adherence to a Middle Eastern version of the MD.[39] Moreover, to our knowledge, this is the first study conducted in Lebanon that discusses the association between HTN and dietary and psychological factors, as well as highlight the divergent factors associated in men and women.

On the other hand, there were some limitations that must be addressed. First, given the cross-sectional design of our study, it was difficult to establish a causal relationship between HTN and the studied factors. In fact, participants may have modified their lifestyle habits in response to raised BP, introducing a reverse-causality bias. This study design may as well be susceptible to misclassification bias when relying on the participants to report risk factors; as a consequence, this may underestimate smoking status and psychological distress, influencing the lack of association between smoking and BDS-22 on HTN and SBP. Second, current practice guidelines recommend that the diagnosis of HTN be based on at least 2 BP measurements per visit (which was done) and on at least 2 visits, which is not feasible in large population studies. Although this might influence the prevalence of HTN, this approach is supported and commonly adopted in epidemiological studies. Third, we did not follow the traditional epidemiologic description of prevalence, awareness, treatment, and control of hypertension, because the survey did not account for the awareness of hypertension in the population. Fourth, BDS-22 measures overall psychological distress and we suggest that further research includes a number of instruments to measure different and multiple stress factors (environmental, psychological, and biological). Finally, the LMDS index is based on a non-quantitative food frequency questionnaire, making the components equally weighed and similarly scored from 0 to 4, giving all foods same effect on HTN and BP, which may not be true. In addition, we did not account for intake of salt and alcohol[19] and were unable to take into account total energy intake. Nevertheless, this type of dietary index is simple and has been extensively used in previous epidemiological studies.

6 | CONCLUSIONS

This study has shown that in Lebanon, HTN and poor BP control are highly prevalent. We also found that the risk factors of HTN were age, BMI, and previous CVD, with other factors marginally associated with HTN in both genders. In this respect, we consider that prevention of HTN at the population level should mainly focus on overweight prevention by emphasizing nutritional and physical activity policies. Last, results of our study provide public health agencies in Lebanon additional evidence of the burden of HTN in the country and should encourage them to develop national health programs focusing on improving the treatment and control of HTN in Lebanon.

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CONFLICT OF INTEREST

The authors report no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Article 2 (Published)

Title: Unhealthy Behavior and Risk of Hypertension – The CONSTANCES Population Based Cohort

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Abstract:

Background: The prevalence of hypertension (HTN) is reaching epidemic proportions globally. Among other factors, unhealthy behaviors may contribute to this increasing prevalence. However population-based studies are needed to evaluate and quantify the extent to which these factors are determinants of HTN.

Objectives: We aimed to evaluate the individual and combined association between unhealthy behavior and hypertension.

Methods: We conducted cross-sectional analysis using data from the population based cohort study CONSTANCES. Blood pressure measurements were taken based on standardized operational procedures. Prevalent HTN was defined by a SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg or by individuals who were currently taking antihypertensive medications. Lifestyle behaviors were assessed through validated self-administered questionnaires. Alcohol consumption was determined taking into consideration overall as

well as weekly alcohol intake. Physical activity was assessed considering the type and frequency of leisure time and sports activities. Dietary adherence was done following the dietary approach to stop hypertension diet. We considered heavy alcohol drinking, sedentary level physical activity, low/medium dietary adherence, and overweight/obesity as unhealthy behaviors. Participants' characteristics were compared according to the number of unhealthy behaviors and the association between hypertension and unhealthy behaviors was estimated using logistic regression.

Results: A total of 86,448 volunteer participants were included and the prevalence of hypertension was of 31.1%. Of those with hypertension, 8.2%, 33.0%, 44.3% and 14.5% exhibited 0, 1, 2 or ≥3 unhealthy behaviors respectively. In both sexes, the prevalence of hypertension increased with low/medium dietary adherence compared to high ($p < 0.01$), in overweight/obese compared to normal body mass index ($p < 0.001$), with heavy alcohol consumption compared to moderate or never ($p<0.05$) and with sedentary physical activity level compared to high in women only ($p=0.049$). Combination of several unhealthy behaviors was associated with increased odds of hypertension (p trend <0.001); men reporting 2 or ≥3 unhealthy behaviors had an adjusted odds ratio (ORa) of hypertension of 1.77 and 2.29 respectively, while women had an ORa of 1.71 and 2.14, respectively.

Conclusion: Individual and combined unhealthy lifestyle factors were strongly associated with hypertension in this large population-based study.

Keywords: Epidemiology, hypertension, lifestyle behavior, DASH diet, alcohol consumption, physical activity, body mass index

Original Article

Unhealthy behavior and risk of hypertension: the CONSTANCES population-based cohort

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Objectives: We aimed to evaluate the individual and combined association between unhealthy behavior and hypertension (HTN).

Methods: We conducted cross-sectional analysis using data from the population-based cohort study CONSTANCES. Blood pressure measurements were taken based on standardized operational procedures. Dietary adherence was done following the dietary approach to stop HTN diet. We considered heavy alcohol drinking, sedentary-level physical activity, low/medium dietary adherence and overweight/obesity as unhealthy behaviors. Participants' characteristics were compared according to the number of unhealthy behaviors and the association between HTN and unhealthy behaviors was estimated using logistic regression.

Results: A total of 86 448 volunteer participants were included and the prevalence of HTN was of 31.1%. Of those with HTN, 8.2, 33.0, 44.3 and 14.5% exhibited 0, 1, 2 or at least 3 unhealthy behaviors, respectively. In both sexes, the prevalence of HTN increased with low/medium dietary adherence compared with high ($P < 0.01$), in overweight/obese compared with normal BMI ($P < 0.001$), with heavy alcohol consumption compared with moderate or never ($P < 0.05$) and with sedentary physical activity level compared to high in women only ($P = 0.049$). Combination of several unhealthy behaviors was associated with increased odds of HTN (P trend < 0.001); men reporting 2 or at least 3 unhealthy behaviors had an adjusted odds ratio of HTN of 1.77 and 2.29, respectively, while women had an adjusted odds ratio of 1.71 and 2.14, respectively.

Conclusion: Individual and combined unhealthy lifestyle factors were strongly associated with HTN in this large population-based study.

Keywords: alcohol consumption, BMI, dietary approach to stop hypertension diet, epidemiology, hypertension, lifestyle behavior, physical activity

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; CNAMTS, Caisse nationale d'assurance maladie des travailleurs salariés; CONSTANCES, cohorte des CONSulTANts des Centre d'examens de sante de la Securite sociale; CVD, cardiovascular disease; DASH, dietary approach to stop hypertension; HSC, health-screening center; HTN, hypertension; ORa, adjusted odds ratio

INTRODUCTION

Hypertension (HTN) is the most common chronic disease and the leading risk factor for cardiovascular diseases (CVD). Globally, HTN affects more than 1 billion individual, and the prevalence is expected to increase by 15–20% by 2025 [1,2]. As such, HTN has become an important global public health challenge. Although the pathogenesis of primary HTN is not completely understood, it originates from a combination of genetic and environmental factors, with an increasing prevalence attributed to population growth, ageing and behavioral risk factors [3]. Even though the genetic predisposition to HTN is nonmodifiable and conveys lifelong CVD risk, the risk for HTN is modifiable and largely preventable due to a strong influence by key lifestyle factors. In fact, a number of epidemiological studies describe an apparent relationship between blood pressure (BP) and lifestyle behaviors [4,5], leading to common lifestyle modifications recommendations in worldwide guidelines for the prevention and management of HTN [5,6]. These lifestyle measures include salt restriction, moderation of alcohol consumption, adoption of a quality diet rich in fruits and vegetables, engagement in regular

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physical activity and weight reduction aiming at maintaining a normal range BMI. Observational studies have shown that these lifestyle modifications were independently associated with BP reductions, regardless of other factors [7]. In addition, some suggest that these factors may be interrelated, thus a combination of behavioral factors may provide additional BP reductions [6–8]. One randomized trial, described the value of the Dietary Approach to Stop Hypertension (DASH) diet in reducing BP and reported a significant 'added value' associated with exercise and weight loss in the context of the DASH diet [8]. A recent meta-analysis also found that this combination of interventions including weight loss, diet and physical activity to be associated with further BP reductions compared with individual modifications [9]. However, to our knowledge, few studies evaluated the combined association of unhealthy behaviors on the prevalence of HTN. In fact, a quantification of the individual and combined associations of unhealthy behavior on the prevalence of HTN warrants further evaluation, especially from a large population-based perspective. The French nationwide, large cohort CONSTANCES (cohorte des CONSulTANts des Centre d'examens de sante de la Securite sociale) [10] represents a major opportunity to provide further epidemiologic data on this subject. Therefore, we conducted this study to examine the individual and combined associations between unhealthy behaviors, specifically, nonadherence to dietary recommendations, low physical activity, overweight and heavy alcohol consumption, with HTN from the CONSTANCES study. We aimed to evaluate the quantitative extent to which modifiable lifestyle factors are determinants of HTN to assess the magnitude of potential primary prevention.

METHODS

Study design and study population

The ancillary study is a cross-sectional analysis using data from the CONSTANCES study. The general aim of CONSTANCES is to establish a large population-based cohort to contribute to the development of epidemiologic research (http://www.constances.fr/index_EN.php). Details about the study design and methods have been extensively discussed [10,11]. In brief, CONSTANCES is an ongoing prospective cohort that started in 2012 and plans to include 200 000 participants by 2019. Adults aged 18–69 at inception were randomly selected from the National Health Insurance Fund (CNAMTS; Caisse nationale d'assurance maladie des travailleurs salariés) that covers salaried workers, professionally active or retired and their dependents (more than 85% of the French population) following a sampling scheme stratified on age, sex, socioeconomic status and region of France to ensure a representative sample of the CNAMTS.

Data collection

At enrollment, volunteer participants completed self-administered questionnaires where social, demographic, health information including personal and family history of diseases and events, and lifestyle behavior characteristics were gathered. In addition, they presented to the nearest of the 22 selected health-screening centers (HSCs) located throughout France, to benefit from a comprehensive health examination whereby medical, paraclinic exams, anthropometric measurements and biologic tests were performed. Furthermore, participants were linked through national social and health administrative databases, through which detailed information concerning occupational status as well as health events and medical acts (medication, hospitalization...) were noted. All participants signed an informed consent and the CONSTANCES cohort was authorized by the French National Data Protection Authority (Commission nationale de l'informatique et des libertés) and approved by the National Medical Council, and the Institutional Review Board of the National Institute for Medical Research-Institut national de la santé et de la recherche médicale (French National Institute of Health and Medical Research).

Study participants

Between February 2012 and January 2018, a total of 87 808 volunteer participants were recruited and linked to the French health insurance administrative database. Of them we excluded 1360 with low BMI (BMI $< 18\,kg/m^2$). We therefore analyzed 86 448 volunteer participants.

Hypertension and blood pressure control definition

BP measurements were taken during the clinical examination at the HSC based on standardized operational procedures [12]. SBP and DBP were measured in each arm at 2 min interval after 5 min of rest and using an automated oscillometric sphygmomanometer. The arm giving the highest SBP was considered the reference arm and a third BP measure was taken after 1 min of rest, the average of these two measurements was considered. Prevalent HTN was defined by a SBP at least 140 mmHg and/or a DBP at least 90 mmHg or by individuals taking antihypertensive medications [5].

Behavioral risk factors definitions

Lifestyle behavior was assessed through validated self-administered questionnaires.

Alcohol consumption was determined considering the quantity and type of alcoholic beverages consumed the previous week [13]. We subsequently defined alcohol consumption as never/light (0–3 glass/week (0–30 g/week) for men and 0–2 [0–20 g/week) for women], moderate [4–21 (40–210 g/week) glass/week for men and 3–14 (30–140 g/week) for women] and heavy drinkers [>21 glass/week (>210 g/week) for men and >14 (>140 g/week) for women] [14]. Heavy drinking was considered an unhealthy behavior.

Physical activity was assessed through questions related to the type and frequency of leisure time/sports and transferring (walking, biking...) activities [15], then a score of 0–6 was calculated and physical activity level was classified as sedentary (0–2), moderately active (3–4) and highly active (5–6). Sedentary level was considered an unhealthy behavior.

Dietary assessment was done through a validated 52-items food frequency questionnaire from which a DASH score was constructed based on food groups described by Fung *et al.* [16]. The score considers eight food and nutrients for which consumption was divided into quintiles, and participants' intakes were assigned 1–5 points according to a sex-specific intake ranking [16,17]. Dietary components for which consumption should be increased (fruits, vegetables, nuts and legumes, low-fat dairy, whole grains) were rated on a scale of 1–5; the higher the score, the more frequent the consumption of that food. Dietary constituents for whom low consumption is desired (sodium, sweetened beverages, red and processed meats), were scored on a reverse scale, with lower consumption receiving higher scores. Component scores were summed, and an overall DASH score ranging from 8 to 40 was calculated. Overall DASH score was subsequently collapsed to tertiles for analysis; higher tertile indicating a higher dietary quality and dietary adherence categorized into low (<20 for men and <21 for women), medium (20–29 for men and 21–30 for women) and high (≥30 for men and ≥31 for women). We considered low/medium dietary adherence an unhealthy behavior.

BMI (kg/m^2) was calculated at the HSC. Weight and height were measured with a scale and a measuring rod without shoes, respectively. It was then categorized into three classes: normal (≤25 kg/m^2), overweight (25 kg/m^2 < BMI < 30 kg/m^2), and obese (≥30 kg/m^2). We considered overweight/obese (BMI > 25 kg/m^2) an unhealthy behavior.

Accordingly, unhealthy behaviors were considered as heavy alcohol consumption, sedentary-level physical activity, low/medium dietary adherence and overweight/obese. Participants could exhibit 0 (none), 1, 2, 3 or 4 unhealthy behaviors; we combined those with 3 or 4 unhealthy behaviors to ensure adequate sample size.

Covariates

Education level was collected according to the International Standard Classification of Education [18] and was then classified into three levels: High school diploma or less (≤13 years of education), undergraduate degree (14–16 years of education) and postgraduate degree (≥17 years of education). Marital status was categorized into couple life or single (including widowed or separated/divorced). Household monthly income was categorized into: less than 1000; 1000–2099; 2100–4199; at least 4200 Euros per month.

Diabetes mellitus status was based on either self-reported type II diabetes, receiving anti-diabetic medication or a fasting blood glucose concentration greater than or equal to 7 mmol/l. Dyslipidemia was defined as having hypercholesterolemia and/or hypertriglyceridemia; either recorded by the health care practitioner at the HSC or by a fasting plasma total-cholesterol or triglycerides level of at least 6.61 mmol/l (255 mg/dl) or more than 1.7 mmol/l (150 mg/dl), respectively. History of CVD was considered as any self-reported previous diagnosis of angina pectoris, myocardial infarction, cerebrovascular accident or peripheral artery disease [5].

Statistical analysis

Descriptive analysis was performed using counts and percentages or mean ± SD. Each characteristic was compared between participants with and without HTN using logistic regressions adjusted for age and sex. In addition, we compared characteristics of participants according to the number of unhealthy behaviors using logistic regressions adjusted for age and stratified by sex. Also with logistic models, we estimated the association between prevalent HTN and unhealthy behaviors. In a first step, models were adjusted for age, education and monthly income (Model 1). In a second step, models were further adjusted for diabetes and dyslipidemia (Model 2). We first performed separate models for each unhealthy behavior using categorical variables and binary variables. Then, we examined the association between HTN and the number of unhealthy behaviors (0–≥3) independently associated with HTN. Adjusted odds ratios (ORa) were presented along with 95% confidence interval (CI), all statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and P of 0.05 or less was considered significant.

RESULTS

Baseline characteristics of participants

The baseline characteristics of the studied participants are presented in Table 1. Of the total population, 52.6% were females and the mean ± SD age was of 47.9 ± 13.4; it was higher in those with HTN compared with those without (56.0 ± 11.2 vs. 44.2 ± 12.6, respectively; $P < 0.001$). Unhealthy behaviors were notable among participants; around 40.7% of the participants were overweight or obese (BMI ≥ 25), 9.9% were sedentary, 77.2% did not highly adhere to dietary guidelines and 11.1% heavily consumed alcohol. The prevalence of HTN was 31.3% and it was more common in men than in women (40.4 vs. 23.1%, respectively, $P < 0.001$). Among the 27 016 individuals with HTN, 10 710 (39.6%) were receiving antihypertensive medication.

Characteristics and unhealthy behaviors

The proportion of unhealthy behavior(s) in participants with and without HTN presented by sex is illustrated in Fig. 1. Also, participants' characteristics according to the number of unhealthy behaviors stratified by sex are presented in Tables 2 and 3. Overall, unhealthy behaviors were more frequent in men (13.1 vs. 5.7% had three or more unhealthy behaviors; $P < 0.001$). Of those with HTN, 8.2, 33.0, 44.3 and 14.5% exhibited 0, 1, 2 or at least 3 unhealthy behaviors, respectively. Age-adjusted, sex-stratified analysis revealed minimal differences between men and women. In men, a higher mean age was seen in those with increased number of unhealthy behavior, while in both sexes a higher number of unhealthy behaviors was associated with lower education ($P < 0.001$), lower household monthly income ($P < 0.001$), current smoking status ($P < 0.001$) and presence of any of diabetes, history of CVD or dyslipidemia ($P < 0.001$).

TABLE 1. Participants' characteristics according to hypertension status

Characteristic	All participants, *n* (%)	Participants without HTN, *n* (%)	Participants with HTN, *n* (%)	*P* value
Overall	86 448	59 432 (68.7)	27 016 (31.3)	
Sex				<0.001
Male	40 974 (47.4)	24 437 (41.1)	16 537 (61.2)	
Female	45 474 (52.6)	34 995 (58.9)	10 479 (38.8)	
Age (years)				<0.001
18–39	26 412 (30.5)	23 645 (39.8)	2767 (10.2)	
40–49	20 082 (23.2)	15 921 (26.8)	4161 (15.4)	
50–59	19 586 (22.7)	11 773 (19.8)	7813 (28.9)	
≥60	20 368 (23.6)	8093 (13.6)	12 275 (45.4)	<0.001
SBP (mmHg)	129.9 ± 16.4	122.0 ± 9.9	147.2 ± 14.5	<0.001
DBP (mmHg)	76.9 ± 9.7	73.2 ± 7.3	85.0 ± 9.4	
Education level				<0.001
≤High school diploma	22 803 (26.4)	12 229 (20.6)	10 574 (39.1)	
Undergraduate degree	13 842 (16.0)	9459 (15.9)	4384 (16.2)	
Postgraduate degree	49 802 (57.6)	37 744 (63.5)	12 058 (44.6)	
Income of the house/month				<0.001
Less than 1000€	4121 (4.8)	2948 (5.0)	1173 (4.3)	
1000–2099€	16 769 (19.4)	11 426 (19.2)	5343 (19.8)	
2100–4199€	41 115 (47.6)	27 892 (46.9)	13 223 (49.0)	
More or equal than 4200€	24 443 (28.3)	17 166 (28.9)	7277 (26.9)	
Familial situation				<0.001
Single	23 089 (26.7)	16 662 (28.0)	6427 (23.8)	
Couple life	63 359 (73.3)	42 770 (72.0)	20 589 (76.2)	
BMI (kg/m^2)	25.1 ± 4.3	24.2 ± 3.9	27.1 ± 4.7	<0.001
BMI class				<0.001
<25	48 498 (56.1)	38 817 (65.3)	9681 (35.8)	
25.0–29.9	27 223 (28.3)	16 005 (26.9)	11 218 (41.5)	
≥30.0	10 727 (12.4)	4610 (7.8)	6117 (22.6)	
Physical activity				<0.001
Sedentary	8561 (9.9)	5938 (10.0)	2623 (9.7)	
Moderate	34 054 (39.4)	24 152 (40.6)	9902 (36.7)	
High	43 833 (50.7)	29 342 (49.4)	14 491 (53.6)	
DASH score	25.9 ± 3.7	25.9 ± 3.7	25.8 ± 3.8	0.057
DASH categories				0.041
Low	5480 (6.3)	3709 (6.2)	1771 (6.6)	
Medium	61 316 (70.9)	42 096 (70.8)	19 220 (71.1)	
High	19 652 (22.7)	13 627 (22.9)	6025 (22.3)	
Alcohol consumption				<0.001
Never/Light	14 334 (16.6)	10 239 (17.2)	4095 (15.1)	
Moderate	62 480 (72.3)	43 475 (73.2)	19 005 (70.4)	
Heavy	9634 (11.1)	5718 (9.6)	3916 (14.5)	
Smoking status				<0.001
Nonsmoker	42 590 (49.3)	29 818 (50.2)	12 772 (47.3)	
Current smoker	15 569 (18.0)	12 001 (20.2)	3568 (13.2)	
Exsmoker	28 289 (32.7)	17 613 (29.6)	10 676 (39.5)	
History of CV events	2064 (2.4)	432 (0.7)	1632 (6.0)	<0.001
Diabetes	3540 (4.1)	982 (1.7)	2558 (9.5)	<0.001
Dyslipidemia	27 076 (31.3)	13 704 (23.1)	13 372 (49.5)	<0.001

Data are mean ± SD for quantitative variables or percent for categorical. *P* from logistic regression model adjusted for age and sex. CV, cardiovascular; DASH, dietary approach to stop hypertension; HTN, hypertension.

Hypertension and unhealthy behaviors

Figure 2 illustrates the significant increased odds of HTN with an increased number of unhealthy behaviors seen across all age categories ($P < 0.001$ for all), whereby a apparently linear relationship exist, reaching more than four-fold increase in the odds of HTN with three or more behaviors in all groups. In addition, the association between HTN and individual and combined unhealthy behavior is reported in Table 4 for men and Table 5 for women. In both sexes, after adjustment for age, education and monthly income (Model 1), HTN was significantly associated with dietary adherence ($P < 0.001$ for men; $P < 0.01$ for women), physical activity ($P < 0.05$ for both), BMI ($P < 0.001$ for both), alcohol consumption ($P < 0.001$ in men) and the number of unhealthy behaviors ($P < 0.001$ for both). After further adjustment for characteristics significantly associated with the number of unhealthy behaviors (Model 2: Model 1 and diabetes and dyslipidemia) most associations remained significant except for physical activity ($P > 0.05$ for both sexes).

Regarding dietary adherence, men and women reporting low to medium dietary adherence had respectively, a 1.18-fold (ORa 1.18, 95% CI 1.06–1.36) and 1.11-fold (ORa 1.11, 95% CI 1.04–1.19) increase of the odds of HTN compared with those with high adherence. Similarly, compared with a lower BMI, overweight and obese men and women had

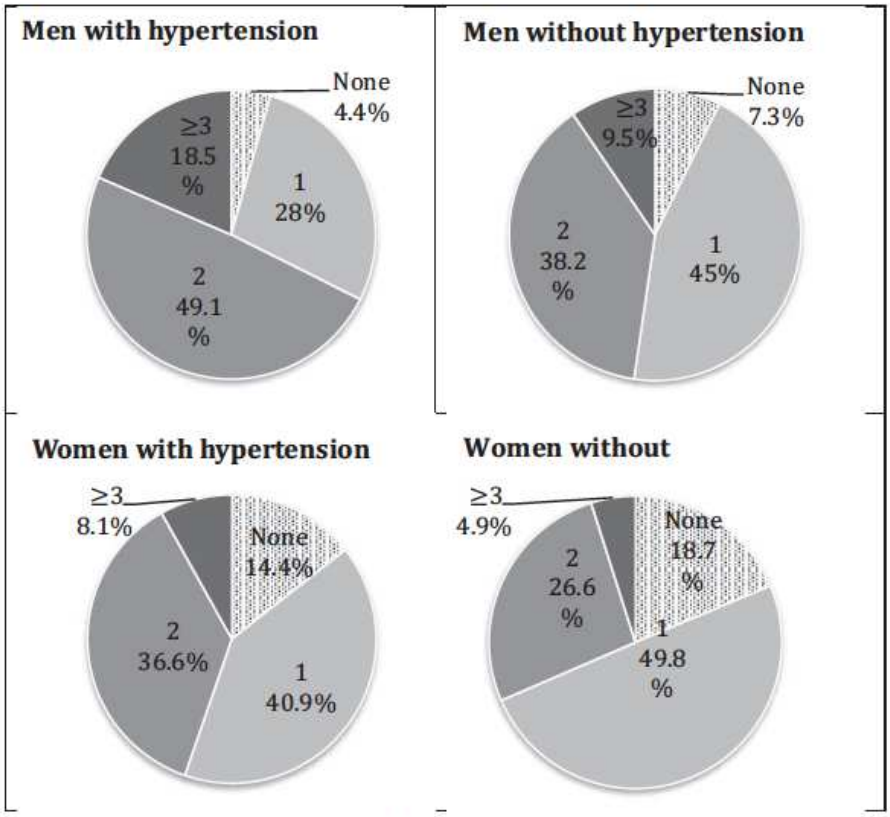

FIGURE 1 Proportion of participants by number of unhealthy behaviors stratified by sex.

respectively, 1.98-fold (1.88–2.09) and 1.87-fold (1.76–1.99) increase of the odds of HTN. Heavy alcohol consumption increased the odds of HTN in men by 1.31-fold (1.22–1.61), however in women, the association did not reach statistical significance compared with never drinking but there was a 1.12-fold increase in the odds of HTN (1.01–1.24) when dichotomizing the variable and comparing heavy drinking to moderate/light drinking. As for physical activity, there was no significant association between sedentary level physical activity and HTN in both sexes ($P=0.749$ for men and $P=0.127$ for women), but in women the association was barely significant when comparing moderate or sedentary level to high level physical activity ($P=0.049$).

Lastly, the frequency of HTN increased with the number of unhealthy behaviors in both sexes. Men reporting two and three-or-more unhealthy behaviors had 1.77-fold and 2.29-fold increase of the odds of HTN respectively, while women had 1.71-fold and 2.14-fold increase, respectively.

DISCUSSION

From this large population-based study, modifiable unhealthy behaviors such as nonadherence to dietary recommendations, overweight, heavy alcohol consumption and low level of physical activity were associated with increased risk of HTN, after adjustment for sociodemographic characteristics and cardiovascular risk factors. The odds of HTN increased with the number of unhealthy behavior. Individuals with three unhealthy behaviors had more than two-fold increased odds of HTN compared with those without unhealthy behavior. To our knowledge, our results are among the few studies to quantitatively estimate the individual and combined associations between lifestyle risk factors and HTN.

Overweight and obesity

We found overweight and obesity (BMI > 25 kg/m^2) to be the strongest unhealthy behavior associated with HTN, increasing its odds by around two-fold in both sexes. These results are consistent with studies in various populations, reporting BMI as the main contributory modifiable factor of BP level [19], finding BMI as the most important lifestyle factor significantly associated with HTN in both sexes [20], and demonstrating a direct, nearly linear association between BMI with BP [19,20]. Similarly, we found a seemingly gradual increase in the odds of HTN, whereby obesity has approximately twice the odds of increasing HTN than overweight, compared with a normal BMI. Our findings further ascertain the association between BMI and HTN and highlight the magnitude of the effect of an elevated BMI on the risk of HTN. These results support recommendations

TABLE 2. Men's characteristics according to the number of unhealthy behaviors

Number of unhealthy behaviors	0	1	2	3 or more	*P* value
Overall, *n* (%)	2496 (6.1)	15631 (38.2)	17468 (42.6)	5379 (13.1)	–
Hypertension	721 (28.9)	4629 (29.6)	8126 (46.5)	3061 (56.9)	<0.001
SBP	132.0 ± 14.8	132.3 ± 14.1	137.5 ± 14.9	140.2 ± 15.4	<0.001
DBP	76.3 ± 9.1	76.8 ± 9.2	80.6 ± 9.5	82.6 ± 9.7	<0.001
Age (year)	49.0 ± 13.3	46.1 ± 13.6	49.9 ± 12.7	51.6 ± 12.4	<0.001
Age categories					<0.001
18–39	719 (28.8)	5804 (37.1)	4222 (24.2)	1080 (20.1)	
40–49	537 (21.5)	3561 (22.8)	4169 (23.9)	1143 (21.3)	
50–59	569 (22.8)	3056 (19.6)	4362 (25.0)	1491 (27.7)	
≥60	671 (26.9)	3210 (20.5)	4715 (27.0)	1665 (31.0)	
Education level					<0.001
≤High school diploma	451 (18.1)	3632 (23.2)	6033 (34.5)	2177 (40.5)	
Undergraduate degree	283 (11.3)	2263 (14.5)	2773 (15.9)	819 (15.2)	
Postgraduate degree	1762 (70.6)	9736 (62.3)	8662 (49.6)	2383 (44.3)	
Income of the house/month					<0.001
Less than 1000€	89 (3.6)	672 (4.3)	726 (4.2)	344 (6.4)	
1000–2099€	312 (12.5)	2483 (15.9)	3081 (17.6)	1182 (22.0)	
2100–4199€	1055 (42.3)	7361 (47.1)	8549 (48.9)	2433 (45.2)	
More or equal than 4200€	1040 (41.7)	5115 (32.7)	5112 (29.3)	1420 (26.4)	
Familial situation					0.002
Single	601 (24.1)	3841 (24.6)	3711 (21.2)	1355 (25.2)	
Couple life	1895 (75.9)	11790 (75.4)	13757 (78.8)	4024 (74.8)	
BMI (kg/m^2)	22.6 ± 1.6	23.5 ± 2.8	27.3 ± 3.6	28.8 ± 3.7	<0.001
BMI class					<0.001
<25	2496 (100)	13286 (85.0)	3387 (19.4)	234 (4.4)	
25.0–29.9	0 (0)	1834 (11.7)	10834 (62.0)	3611 (67.1)	
≥30.0	0 (0)	511 (3.3)	3247 (18.6)	1534 (28.5)	
Physical activity					<0.001
Sedentary	0 (0)	140 (0.9)	1595 (9.1)	2693 (50.1)	
Moderate	817 (32.7)	6578 (42.1)	7497 (42.9)	1204 (22.4)	
High	1679 (67.3)	8913 (57.0)	8376 (48.0)	1482 (28.5)	
DASH score	30.43 (1.51)	25.38 (3.57)	24.17 (3.18)	23.09 (3.32)	<0.001
DASH categories					<0.001
Low	0 (0)	1024 (6.6)	1758 (10.1)	944 (17.5)	
Medium	0 (0)	11959 (76.5)	15208 (87.1)	4410 (82.0)	
High	2496 (100)	2648 (16.9)	502 (2.8)	25 (0.5)	
Alcohol consumption					<0.001
Never/Light	361 (14.5)	1940 (12.4)	2048 (11.7)	417 (7.8)	
Moderate	2135 (85.5)	13528 (86.6)	13126 (75.1)	1632 (30.3)	
Heavy	0 (0)	163 (1.0)	2294 (13.1)	3330 (61.9)	
Smoking status					<0.001
Nonsmoker	1379 (55.2)	7847 (50.2)	7140 (40.9)	1711 (31.8)	
Current smoker	266 (10.7)	2770 (17.7)	3403 (19.5)	1344 (25.0)	
Exsmoker	851 (34.1)	5014 (32.1)	6925 (39.7)	2324 (43.2)	
History of CV events	68 (2.7)	412 (2.6)	698 (4.0)	319 (5.9)	<0.001
Diabetes	54 (2.2)	457 (2.9)	1273 (7.3)	576 (10.7)	<0.001
Dyslipidemia	580 (23.2)	4221 (27.0)	7750 (44.4)	2907 (54.0)	<0.001
Antihypertensive medication	213 (8.5)	1480 (9.5)	3046 (17.4)	1293 (24.0)	<0.001

Data are mean ± SD for quantitative variables or percent for categorical. *P* from logistic regression model adjusted for age. CV, cardiovascular; DASH, dietary approach to stop hypertension.

from worldwide guidelines to maintain a healthy BMI (≤25 kg/m^2), with efforts of preventing and improving the control of HTN [5].

Dietary nonadherence

In our study, low and medium dietary adherence was found to increase the odds of HTN. Numerous studies linked the effect of individual nutrients and foods on the BP [19,21], while others focused on the relationship between a global dietary pattern and BP, considering that dietary components may interact with each other. As such, adopting a DASH-diet has shown to reduce the BP [22,23]; Harrington et al found a dose-response effect between high DASH quintiles (high-quality diet) and SBP in both clinic BP and ambulatory BP monitoring (ABPM) recordings, reporting a difference in clinic SBP of 7.5 and 5.1 mmHg and a difference in ABPM SBP of 6.3 and 5.4 mmHg in men and women, respectively [23]. Furthermore, findings of recent studies demonstrated that adherence to a DASH-style diet was associated with reduced risk of incident HTN [24], particularly comparing quartile 4 to quartile 1 [25]. Our results provide further evidence of the association between a DASH-style diet and HTN while quantifying the magnitude of the effect of the association. These findings, further

TABLE 3. Women's characteristics according to the number of unhealthy behaviors

Number of unhealthy behaviors	0	1	2	3 or more	*P* value
Overall, *n* (%)	8052 (17.7)	21696 (47.7)	13136 (28.9)	2590 (5.7)	–
Hypertension	1510 (18.8)	4281 (19.7)	3835 (29.2)	853 (32.9)	<0.001
SBP	123.1 ± 16.0	123.3 ± 15.6	127.4 ± 16.2	129.0 ± 15.9	<0.001
DBP	73.1 ± 8.9	74.0 ± 9.1	76.5 ± 9.4	78.2 ± 9.2	<0.001
Age (year)	49.3 ± 13.0	46.4 ± 13.5	47.5 ± 13.6	47.9 ± 13.1	<0.001
Age categories					<0.001
18–39	2154 (26.7)	7558 (34.8)	4134 (31.5)	741 (28.6)	
40–49	1792 (22.3)	5182 (23.9)	3039 (23.1)	659 (25.5)	
50–59	2052 (25.5)	4514 (20.8)	2925 (22.3)	617 (23.8)	
≥60	2054 (25.5)	4442 (20.5)	3038 (23.1)	573 (22.1)	
Education level					<0.001
≤High school diploma	1296 (16.1)	4545 (20.9)	3875 (29.5)	794 (30.7)	
Undergraduate degree	1153 (14.3)	3639 (16.8)	2464 (18.8)	449 (17.3)	
Postgraduate degree	5603 (69.6)	13512 (62.3)	6796 (51.7)	1347 (52.0)	
Income of the house/month					<0.001
Less than 1000€	283 (3.5)	973 (4.5)	838 (6.4)	196 (7.6)	
1000–2099€	1340 (16.6)	4407 (20.3)	3307 (25.2)	657 (25.4)	
2100–4199€	3753 (46.6)	10488 (48.3)	6279 (47.8)	1197 (46.2)	
More or equal than 4200€	2676 (33.2)	5828 (26.9)	2712 (20.6)	540 (20.8)	
Familial situation					<0.001
Single	2371 (29.5)	6304 (29.1)	4050 (30.8)	856 (33.1)	
Couple life	5681 (70.5)	15392 (71.0)	9086 (69.2)	1734 (66.9)	
BMI (kg/m^2)	21.8 ± 1.8	23.2 ± 3.8	27.3 ± 5.0	29.3 ± 4.8	<0.001
BMI class					<0.001
<25	8052 (100)	17372 (80.1)	3495 (26.6)	176 (6.8)	
25.0–29.9	0 (0)	2973 (13.7)	6455 (49.1)	1516 (58.5)	
≥30.0	0 (0)	1351 (6.2)	3186 (24.3)	898 (34.7)	
Physical activity					<0.001
Sedentary	0 (0)	385 (1.8)	2053 (15.6)	1695 (65.4)	
Moderate	2610 (32.1)	9360 (43.1)	5562 (42.3)	426 (16.5)	
High	5442 (67.6)	11951 (55.1)	5521 (42.0)	469 (18.1)	
DASH score	31.7 (1.6)	26.6 (3.4)	25.2 (3.1)	24.3 (3.1)	<0.001
DASH categories					<0.001
Low	0 (0)	737 (3.4)	755 (5.8)	262 (10.1)	
Medium	0 (0)	15695 (72.3)	11734 (89.3)	2310 (89.2)	
High	8052 (100)	5264 (24.3)	647 (4.9)	18 (0.7)	
Alcohol consumption					<0.001
Never/light	1698 (21.1)	4461 (20.6)	2928 (22.3)	481 (18.6)	
Moderate	6354 (78.9)	16680 (76.9)	8119 (61.8)	906 (35.0)	
Heavy	0 (0)	555 (2.6)	2089 (15.9)	1203 (46.4)	
Smoking status					<0.001
Nonsmoker	4630 (57.5)	11840 (54.6)	6851 (52.1)	1192 (46.0)	
Current smoker	908 (11.3)	3780 (17.4)	2517 (19.2)	581 (22.4)	
Exsmoker	2514 (31.2)	6076 (28.0)	3768 (28.7)	817 (31.6)	
History of CV events	92 (1.1)	215 (1.0)	220 (1.7)	40 (1.5)	<0.001
Diabetes	85 (1.1)	380 (1.7)	560 (4.3)	155 (6.0)	<0.001
Dyslipidemia	1766 (21.9)	4761 (21.9)	4132 (31.5)	959 (37.0)	<0.001
Antihypertensive medication	581 (7.2)	1803 (8.3)	1890 (14.4)	404 (15.6)	<0.001

Data are mean ± SD for quantitative variables or percent for categorical. *P* from logistic regression model adjusted for age. CV, cardiovascular; DASH, dietary approach to stop hypertension.

suggest that adopting a healthy diet through adherence to dietary recommendations can help in the prevention and management of HTN.

Alcohol consumption

Heavy alcohol consumption was associated with increased odds of HTN compared with moderate or never/light consumption. Notably, the strength of the association is distinct between both sexes, and moderate consumption compared with never/light drinking did not reach statistical significance in both sexes; neither did heavy consumption in females. In fact, heavy alcohol intake and risk of HTN was described in numerous studies and in different population [20,26] and the relationship between light-to-moderate alcohol consumption remains controversial. A meta-analysis of 16 prospective studies assessed sex-specific relationship between alcohol consumption and the risk of developing HTN [27] and found that heavy alcohol consumption more than 20 g/day is associated with the risk of development of HTN in both women and men, while moderate drinking had a trend toward increased risk of HTN in men and a decreased risk in women. In our study, the difference in the magnitude of the effect among sexes

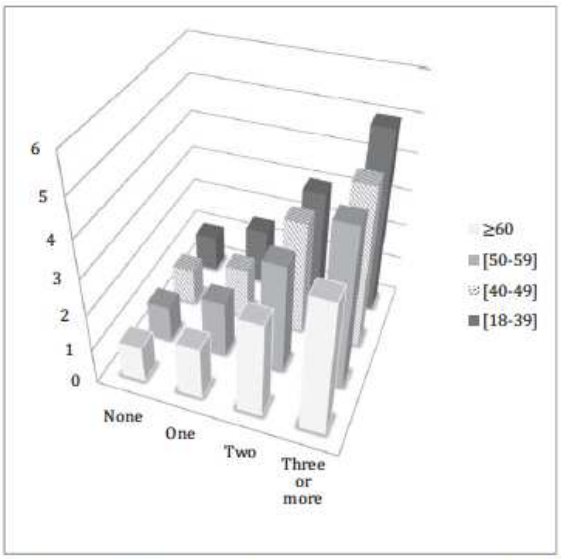

FIGURE 2 Odds of hypertension according to unhealthy behavior among age categories.

could be attributed to the differences in the pattern of drinking and beverages choices, yet the association between heavy intake and HTN was further demonstrated. Accordingly, alcohol consumption should be limited in both men and women [5].

Physical activity

The association between physical activity and HTN was non significant in both sexes; particularly when comparing moderate or sedentary level physical activity to high level (reference). In women, there was a barely significant association when comparing moderate-to-sedentary level physical activity to high level physical activity. Although one previous study also reported lack of association between physical activity and SBP [19], however in general, our results contradict results from observational studies that described a strong and protective effect of physical activity on HTN, and reported an inverse dose-response association between levels of physical activity [28]. This controversy could be explained by the fact that we used a less reproducible physical activity score from the literature, which could have failed to report a reliable estimation of physical activity. The high proportion of participants assessed as high level physical activity (50.7%) supports this hypothesis. In addition, we did not calculate the corresponding metabolic equivalent for the type of reported physical activity, and therefore a different categorization of physical activity could have yielded different results.

Number of unhealthy behaviors

We found a nearly linear association between the number of unhealthy behaviors and HTN; the odds of HTN increased continuously with 1, 2, 3 or more, unhealthy behaviors. Epidemiologic studies have shown that modifiable lifestyle factors are independently associated with HTN, but to our knowledge none have examined their cumulative effect. In fact, unhealthy behaviors often clustered, may have synergistic effect of the prevalence of HTN,

TABLE 4. Association between prevalent hypertension and the number of unhealthy behaviors in men

Term	Model 1	*P* value	Model 2	*P* value
DASH		<0.0001		<0.0001
High	1.00 (ref)	–	1.00 (ref)	–
Medium	1.15 [1.07–1.23]	0.0002	1.13 [1.05–1.21]	0.0007
Low	1.37 [1.24–1.53]	<0.0001	1.32 [1.19–1.47]	<0.0001
Low/medium vs. high	1.20 [1.09–1.42]	<0.0001	1.18 [1.06–1.36]	0.0001
Physical activity		0.0489		0.7488
High	1.00 (ref)	–	1.00 (ref)	–
Moderate	1.03 [0.98–1.09]	0.1859	1.00 [0.95–1.06]	0.8398
Sedentary	1.10 [1.02–1.20]	0.0182	1.03 [0.95–1.12]	0.4470
Moderate/sedentary vs. high	1.05 [0.99–1.10]	0.0512	1.01 [0.96–1.06]	0.6617
BMI (kg/m^2)		<0.0001		<0.0001
<25	1.00 (ref)	–	1.00 (ref)	–
25.0–29.9	1.89 [1.80–2.01]	<0.0001	1.81 [1.72–1.91]	<0.0001
≥30.0	3.19 [2.94–3.46]	<0.0001	2.87 [2.65–3.12]	<0.0001
≥25 vs. <25	2.12 [2.01–2.22]	<0.0001	1.98 [1.88–2.09]	<0.0001
Alcohol consumption		<0.0001		<0.0001
Never/light	1.00 (ref)	–	1.00 (ref)	–
Moderate	1.03 [0.96–1.12]	0.3851	1.05 [0.97–1.14]	0.1824
Heavy	1.37 [1.25–1.51]	<0.0001	1.36 [1.24–1.51]	<0.0001
Heavy vs. moderate/never	1.33 [1.25–1.43]	<0.0001	1.31 [1.22–1.61]	<0.0001
No. of unhealthy behaviors		<0.0001		<0.0001
0	1.00 (ref)	–	1.00 (ref)	–
1	1.14 [1.02–1.27]	0.0229	1.11 [0.99–1.24]	0.0560
2	1.89 [1.70–2.11]	<0.0001	1.77 [1.59–1.98]	<0.0001
3 or more	2.54 [2.25–2.87]	<0.0001	2.29 [2.03–2.60]	<0.0001

Model 1: logistic regression model adjusted for age, education level, monthly income and antihypertensive medications. Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, dyslipidemia and antihypertensive medications. DASH, dietary approach to stop hypertension.

TABLE 5. Association between prevalent hypertension and the number of unhealthy behaviors in women

Term	Model 1	*P* value	Model 2	*P* value
DASH		<0.0001		<0.0001
High	1.00 (ref)	–	1.00 (ref)	–
Medium	1.11 [1.04–1.18]	0.0014	1.09 [1.03–1.17]	0.0039
Low	1.52 [1.27–1.81]	<0.0001	1.47 [1.23–1.74]	<0.0001
Low/medium vs. high	1.13 [1.06–1.25]	<0.0001	1.11 [1.04–1.19]	0.00012
Physical activity		0.0430		0.1270
High	1.00 (ref)	–	1.00 (ref)	–
Moderate	1.08 [1.01–1.16]	0.0152	1.07 [1.01–1.14]	0.0427
Sedentary	1.07 [0.95–1.20]	0.2386	1.04 [0.92–1.16]	0.5375
Moderate/sedentary vs. high	1.08 [1.01–1.15]	0.0123	1.06 [1.00–1.13]	0.0490
BMI (kg/m^2)		<0.0001		<0.0001
<25	1.00 (ref)	–	1.00 (ref)	–
25.0–29.9	1.59 [1.49–1.71]	<0.0001	1.54 [1.44–1.65]	<0.0001
≥30.0	3.12 [2.85–3.39]	<0.0001	2.90 [2.66–3.17]	<0.0001
≥25 vs. <25	1.97 [1.86–2.09]	<0.0001	1.87 [1.76–1.99]	<0.0001
Alcohol consumption		0.0631		0.1104
Never/light	1.00 (ref)	–	1.00 (ref)	–
Moderate	0.98 [0.91–1.06]	0.6959	0.99 [0.92–1.08]	0.9588
Heavy	1.11 [0.99–1.26]	0.0701	1.11 [0.99–1.25]	0.0753
Heavy vs. moderate/never	1.13 [1.02–1.25]	0.0204	1.12 [1.01–1.24]	0.0373
No. of unhealthy behaviors		<0.0001		<0.0001
0	1.00 (ref)	–	1.00 (ref)	–
1	1.24 [1.14–1.35]	<0.0001	1.22 [1.12–1.33]	<0.0001
2	1.80 [1.65–1.97]	<0.0001	1.71 [1.57–1.88]	<0.0001
3 or more	2.31 [2.01–2.64]	<0.0001	2.14 [1.87–2.45]	<0.0001

Model 1: logistic regression model adjusted for age, education level, monthly income and antihypertensive medications. Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, dyslipidemia and antihypertensive medications. DASH, dietary approach to stop hypertension.

underlining the importance of examining their combined effect. A systematic review of randomized controlled trials, reported that a combination of interventions including weight loss, diet and physical activity, had the most marked and significant BP reductions compared with individual modifications [9]. The ENCORE study also described the additive effect of lifestyle behaviors on the BP in untreated overweight hypertensive individuals, whereby the addition of exercise and weight loss to the DASH diet resulted in larger BP reductions than DASH diet alone (12.5/5.9 vs. 7.7/3.6 mmHg, respectively; $P < 0.001$) [8]. Furthermore, a prospective study of women studied six modifiable lifestyle variables and found that low-risk combinations of modifiable lifestyle factors were associated with dramatic reductions in the incidence of self-reported HTN during follow-up [24]. In our study, the association between higher number of unhealthy behaviors and the odds of developing HTN, persisted even after adjusting for socioeconomic and cardiovascular risk factors, this indicates that a combination of unhealthy behavior is strongly associated with HTN irrespective of the presence of other risk factors. The present findings suggest that lifestyle changes should employ a multidisciplinary approach that includes weight loss, regular exercise, healthy diet and limitation of alcohol consumption; this approach can offer considerable benefit in the prevention of HTN.

Study strengths and limitations

The main strength of our study is the design of CONSTANCES, which ensure sufficient power; we adopted a population-based approach using a large nationwide randomly selected sample of participants. In addition, we used standardized protocols to collect anthropometric data including BP measurements; this ensures replication of data collection for all volunteers regardless of when, where and by whom they are performed and adds validity to our results [11,12]. Furthermore, data were collected through different reliable methods, using national databases and validated questionnaires and there was a lack of missing data. Another major strength of our study is the exploration of the combined association of unhealthy behaviors and an analysis stratified by sex.

On the other hand, our study had some limitations. First, given the cross-sectional design of the study, it may be difficult to ascertain the temporal order of unhealthy behaviors and HTN. In fact, participants may have modified their lifestyle habits in response to having HTN, which may have consequences for causal inference. In the future, prospective data from CONSTANCES are expected to yield more conclusive results. Second, lifestyle behaviors were self-reported using self-administered questionnaires introducing the possibility of misclassification bias. Third, our study may be susceptible to selection bias, due to the selection effect associated with voluntary participation, also because CONSTANCES covers only salaried workers excluding agricultural and self-employed workers, therefore the population may not be representative of the general population and the frequency of HTN and of unhealthy behaviors may be affected. However, all patient in the CONSTANCES study were enrolled through the same procedure and data collection was similar to all, so we can assume that the error was not differential and was unlikely to have biased the estimation of the association between unhealthy behaviors and HTN.

In conclusion, this study provides further evidence and confirms the association between unhealthy behaviors and HTN, on an individual and combined level. An unhealthy lifestyle, characterized by nonadherence to dietary recommendations, overweight or obesity and heavy alcohol consumption, is associated with greater odds of HTN, which increased with increased number of unhealthy behaviors. From a population-based perspective, these findings of utmost importance, promote that a global healthy lifestyle through improvement of modifiable behaviors could have major benefits in the prevention of HTN.

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Conflicts of interest

There are no conflicts of interest.

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Article 3 (Under review)

Title: Unhealthy behaviors and risk of uncontrolled hypertension among treated individuals-The CONSTANCES population-based study

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Abstract:

Background: Uncontrolled hypertension has been frequently reported among treated hypertensive individuals**.** From an epidemiological standpoint, a quantification of the individual and combined effect of lifestyle factors on uncontrolled blood pressure deserves further evaluation.

Objectives: We aimed to examine the individual and combined associations between unhealthy behaviors, particularly diet, physical activity, alcohol consumption and body mass index with uncontrolled HTN among treated hypertensive adults.

Methods: We conducted a cross-sectional analysis using data from the population based cohort study CONSTANCES. Volunteer participants who have been diagnosed with hypertension, were taking antihypertensive medications and had complete lifestyle behaviors questionnaires were eligible to be included in the study. Those with low BMI (BMI<18kg/m^2) were excluded. BP measurements were taken during the clinical examination based on standardized operational procedures. Uncontrolled BP was defined as mean systolic BP ≥140 mmHg and/or mean diastolic BP ≥90 mmHg. Lifestyle behaviors

were assessed through validated self-administered questionnaires. We considered heavy alcohol drinking, sedentary level physical activity, low/medium dietary adherence to dietary recommendations, and overweight/obesity (BMI ≥25 kg/m2) as unhealthy behaviors. Using logistic regression models we estimated the association between control of hypertension and unhealthy behaviors. Statistical analyses were stratified by sex

Results: A total of 10,710 hypertensive treated volunteer participants were included and 56.1% had uncontrolled hypertension; of them, 2.0%, 24.5%, 54.0% and 19.5% exhibited 0, 1, 2 or ≥3 unhealthy behaviors respectively. In men, there was an increased odds of uncontrolled hypertension with low or medium dietary adherence compared to high ($p<0.05$ for both), with heavy alcohol consumption compared to light/never (adjusted odds ratio 1.34, 95%CI 1.10-1.63) and in overweight or obese compared to normal ($p\leq0.001$ for both). In addition, men reporting a combination of ≥3 unhealthy behaviors compared to none, had an increased odds of hypertension of 1.67 (95% CI 1.09-2.53).

Conclusion: An unhealthy lifestyle, characterized by non-adherence to dietary recommendations, overweight or obesity and heavy alcohol consumption, is associated with uncontrolled hypertension, at the individual and combined level, and particularly in men. Improvement of modifiable behaviors could offer considerable benefits in the management of hypertension.

Keywords: alcohol consumption, body mass index, DASH diet, epidemiology, hypertension, lifestyle behavior, physical activity

INTRODUCTION

Arterial hypertension is a global public health issue affecting more than 1 billion individuals worldwide and causing an estimated ten million deaths every year.[1] Despite the availability of efficient and well-tolerated medications and widespread public health efforts to treat individuals with hypertension, inadequate blood pressure (BP) control is frequently reported among treated hypertensive individuals, and contributes significantly to increased risk of cardiovascular disease (CVD), stroke and chronic kidney disease (CKD).[2]

A number of epidemiological studies commonly reported a high prevalence rate of uncontrolled hypertension at the 140/90mmHg threshold; in the United States, data analysis from the National Health and Nutrition Examination Survey (NHANES) found that among treated individuals around 45% had uncontrolled BP.[3] Within Europe, BP control rate among those treated reached 40% in England, 30% in Germany, 28% in Italy, 19% in Spain and 21% in Sweden.[4] Similarly, the estimated prevalence of hypertension in France is 31% and 51.3% of hypertensive treated patients are not controlled.[5]

A broad range of factors have been identified that contribute to poor BP control. These include, physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled),[6] deficiencies of healthcare systems in their global approach to chronic diseases[7] and low adherence to treatment including antihypertensive prescriptions and lifestyle changes.[8] In addition, factors such as socio-economic characteristics and poor lifestyle behaviors have been described as predictors of poor BP control.[9] Studies suggest that unhealthy lifestyle behaviors including heavy alcohol drinking, lack of physical activity, poor dietary habits and overweight may contribute to inadequate BP control among hypertensive treated individuals.[9,10] Alternatively, lifestyle modifications were associated with BP reductions among hypertensive individuals;[11,12] Appel et al, reported that behavioral interventions including weight loss, increased physical activity, limitation of dietary sodium intake and reduced alcohol consumption, decreased systolic BP by 12.5 mm Hg and diastolic BP by 5.8 mm Hg.[12]

Common non-pharmacological treatment recommendations in worldwide guidelines for the prevention and management of hypertension include diet, salt intake, potassium intake, alcohol consumption, physical activity and weight. However the quantitative or qualitative targets for each of these measures differ across the guidelines.[13,14] This heterogeneity makes their promotion more challenging and justifies the need to conduct further studies evaluating their impact on different populations. In fact, these recommendations emphasize

lifestyle changes based on intervention trials that were especially effective in pre- or hypertensive individuals; hence, the study of their effect in terms of improving BP control in hypertensive treated individuals remains necessary.

As such, from an epidemiological perspective, a quantification of the individual and combined effect of unhealthy behavior on uncontrolled hypertension warrants further evaluation. The French nationwide large population-based study, CONSTANCES[15] represents a major opportunity to contribute to epidemiologic research and to provide further data on this subject. Therefore, we conducted this study to examine the individual and combined associations between unhealthy behaviors, specifically, non-adherence to dietary recommendations, low physical activity, overweight, and heavy alcohol consumption, with uncontrolled hypertension. We aimed to evaluate the quantitative extent to which modifiable lifestyle factors are determinants of uncontrolled hypertension in order to assess the magnitude of their effect in the management of hypertension, from a gender-based perspective.

RESULTS

Baseline characteristics of participants

The baseline characteristics of the studied participants are presented in table 1, and they were compared between subjects with controlled and uncontrolled hypertension. The mean ± SD age of the population was 59.8±8.6. Unhealthy behaviors were notable among participants; around two third of the participants were overweight or obese (BMI ≥ 25), 10.2% were sedentary, 91.3% did not have a high dietary adherence and 15.0% consumed alcohol heavily.

Among the 10710 hypertensive treated participants 6003 had uncontrolled hypertension, reaching a prevalence of poor BP control of 56.1%. Uncontrolled hypertension was more common in men than in women (62.9% vs. 47.9% respectively, $p<0.001$) and with increased age categories with the highest prevalence seen in those more than 65 years old (63.1%). After adjustment to age and gender, uncontrolled hypertension was more frequent in participants with lower education (46.8% vs. 41.3%, $p<0.001$), living in couple (78% vs. 73.8%, $p<0.001$), with diabetes (17.4% vs. 13.1%, $p<0.001$) or with dyslipidemia (62.2% vs. 57%, $p <0.001$). It was less common in those with history of CVD (11.8% vs. 14.7, $p<0.001$). As for lifestyle factors, those who are overweight or obesity and those with heavy alcohol consumption have a significantly higher prevalence of

uncontrolled hypertension (p<0.001 for both variables) while high dietary adherence is associated with lower frequency. Interestingly, inverse associations were seen with physical activity and smoking status, those with high-level physical activity (p=0.008) had more often uncontrolled hypertension, whereas current smokers seem to have more often controlled hypertension (p<0.001). Globally, 56.3% of the study subjects were receiving one anti-hypertensive medication, while 34.3% were on dual therapy and 9.4% were using three medications or more; those with uncontrolled hypertension were less likely to be receiving mono-therapy and more likely to be receiving dual or triple (or more) therapy (p=0.001).

Characteristics and unhealthy behaviors

The proportion of unhealthy behavior(s) in participants with and without uncontrolled hypertension is illustrated in figure 1. Also, participants' characteristics according to the number of unhealthy behaviors stratified by gender are presented in tables 2 and 3. Overall, unhealthy behaviors were more frequent in men (22.7% vs. 11.0% had three or more unhealthy behaviors; p<0.001). Of those with uncontrolled hypertension, 2.0%, 24.5%, 54.0% and 19.5% exhibited 0, 1, 2 or ≥3 unhealthy behaviors respectively. Age-adjusted, gender-stratified analysis revealed minimal differences between men and women. In brief, a higher number of unhealthy behavior was associated with lower education (p<0.001), lower household monthly income (p<0.001), current smoking status (p<0.001), and presence of diabetes or dyslipidemia, (p trend <0.001).

Uncontrolled BP and unhealthy behaviors

The association between uncontrolled hypertension and dietary adherence, physical activity, BMI, alcohol consumption and the number of unhealthy behavior is reported in table 4 for men and in a supplementary table for women. In men, there was no major difference between the associations found after adjustment for age, education and monthly income (Model 1), and after further adjustment for characteristics significantly associated with the number of unhealthy behaviors (Model 2: model 1 plus diabetes and dyslipidemia). In other words, associations found to be significant in model 1 remained significant in model 2. However, in women, the association between individual unhealthy behaviors and uncontrolled hypertension did not reach statistical significance and is available in supplementary table 1.

Regarding dietary adherence, men reporting low and medium dietary adherence had a 1.26-fold (ORa 1.26, 95%CI 1.04-1.53) and 1.41-fold (ORa 1.41, 95%CI 1.11-1.79)

increase of the odds of uncontrolled hypertension compared to those with high dietary adherence. Similarly, compared to a normal BMI, overweight and obese men had respectively, 1.25-fold (1.09-1.43) and 1.57-fold (1.35-1.83) increase of the odds of uncontrolled hypertension. There was a significant association between alcohol consumption and uncontrolled hypertension (p=0.003); men consuming alcohol heavily had an increase of the odds of uncontrolled hypertension compared to light/never drinkers by 1.34-fold (ORa 1.34, 95%CI 1.10-1.63). The association remained significant when dichotomizing the variable and comparing heavy drinking to moderate/light drinking (ORa 1.35, 95%CI 1.09-1.44; p=0.01). In addition there was a significantly increasing age-adjusted mean SBP across light, moderate and heavy drinking in both sexes: in women the mean SBP ± SD across categories was 134.6 ± 4.8, 135.5 ± 4.2 and 136.1 ± 4.2, respectively (p<0.001) and in men it was 134.9 ± 4.6, 135.7 ± 4.0 and 136.4 ± 3.6, respectively (p<0.001). As for physical activity, there was an unexpected inverse relationship between sedentary level physical activity and uncontrolled hypertension. Lastly, the frequency of uncontrolled hypertension increased with the number of unhealthy behaviors in men only (p<0.001). Those reporting three or more unhealthy behaviors had 1.67-fold (1.09-2.53) increase of the odds of uncontrolled hypertension.

DISCUSSION

From this large population-based study, modifiable unhealthy behaviors such as non-adherence to dietary recommendations, overweight and heavy alcohol consumption were associated with increased risk of uncontrolled hypertension in hypertensive treated individuals. The association was significant only in men, and after adjustment for sociodemographic characteristics and cardiovascular risk factors. Also, the odds of uncontrolled hypertension increased with the number of unhealthy behavior, showing a dose-effect relationship. Men with three or four unhealthy behaviors had 1.7-fold increased odds of hypertension compared to those without unhealthy behavior. To our knowledge, our results are among the few studies to quantitatively estimate the individual and combined effect of unhealthy lifestyle and the risk of uncontrolled hypertension in pharmacologically treated patients.

Compared to a normal BMI, we found overweight and obesity to be strongly associated with uncontrolled hypertension in men, increasing its odds by 1.25-fold and 1.57-fold respectively. This association has been described elsewhere; one study in South

Korea conducted on individuals being treated for hypertension and taking regularly their antihypertensive medications, found that overweight patients were less likely to have their BP under control compared with those whose body weight was normal (ORa 0.44; $p<0.05$).[9] Similarly, the Framingham Heart Study reported that among treated subjects, increasing age, obesity and the presence of left ventricular hypertrophy were associated with lack of SBP control. The authors suggested that public health efforts should be directed at achieving goal BP levels especially in patients who are older, are overweight or have target organ damage.[16]

The association between physical activity and uncontrolled hypertension was not significant in women. In men, surprisingly, the multivariable analysis models found a weak but significant inverse association between physical activity and uncontrolled hypertension, whereby moderate and moderate-to-sedentary physical activity level compared to high level (as reference) were negatively associated with uncontrolled hypertension in men. Overall, our results contradict results from observational studies that described a strong relationship between physical activity and BP control. Ham and Young, found that low physical activity (compared to high level) to be associated with poor BP control among hypertensive treated individuals.[9] Other studies argued that moderate intensity aerobic exercise lowers BP in patients with hypertension and reduces the need for antihypertensive medication.[17,18] Although a dose-dependent relationship was not seen in our study, yet we found a protective relationship between moderate level physical activity and uncontrolled hypertension. Our findings could be explained by the fact that we used a less reproducible physical activity score compared to the literature, which could have failed to report a reliable estimation of physical activity. In addition, we did not calculate the corresponding metabolic equivalent (MET) for the type of reported physical activity, and therefore a different categorization of PA could have yielded different results. Further studies are necessary to assess this aspect.

In our study, low and medium adherence to the DASH diet was found to increase the odds of uncontrolled hypertension in men only. Few studies evaluated the association between a dietary approach and BP control in uncontrolled hypertensive individuals. One randomized controlled trial conducted on hypertensive patients with type 2 diabetes and uncontrolled hypertension, demonstrated that a DASH diet combined with increased daily walking promotes a clinically relevant reduction in ambulatory BP monitoring.[19] On the other hand, most research studied the BP lowering effect of a DASH diet in pre-hypertensive

and hypertensive patients. For example, the DASH collaborative research group found that adopting a DASH-diet in patients with hypertension substantially lowers systolic and diastolic blood pressure by 11.4 and 5.5 mmHg, respectively,[20] suggesting that such BP reductions can help in achieving adequate BP control. Our study demonstrated that non-adherence to dietary recommendation is associated with uncontrolled hypertension, while quantifying the magnitude of the effect of the association. Accordingly, our findings suggest that lifestyle modifications involving the adoption of a DASH-style diet offer an important approach in the treatment of hypertension.

We identified a strong association between heavy alcohol consumption and uncontrolled hypertension. Men who drank alcohol heavily had 1.34-fold increase in the odds of poor BP control. This association has been reported in previous studies. Ham et al reported that heavy alcohol consumption defined as consumption of more than 60g for men and 40g for women during a single drinking session, was independently associated with poor BP control at the 140/90 threshold in a sample of hypertensive treated South Koreans.[9] In addition, a number of studies described an apparent and direct association between heavy alcohol drinking and elevated BP[21,22] that can result in exceeding recommended BP goals. One Japanese study found that in heavy drinkers, systolic and diastolic blood pressure was 2.3/2.0 mmHg higher in heavy drinkers than in non-drinkers.[21] The lack of association in women could be attributed to the differences in the pattern of drinking and beverages choices. Yet, the association between heavy intake and hypertension was further demonstrated, and alcohol consumption should be limited in both men and women.[14]

We found a nearly linear association between the number of unhealthy behaviors and hypertension; the odds of hypertension increased continuously with 1, 2, 3 or more, unhealthy behaviors, but reached statistical significance with 3 or more factors. Few epidemiological studies evaluated the role of modifiable lifestyle factors with uncontrolled hypertension, and to our knowledge none have examined their cumulative effect. In fact, unhealthy behaviors often clustered, may have synergistic effect on BP control, underlining the importance of examining their combined effect. In patients with uncontrolled hypertension and type 2 diabetes, the combination of increasing physical activity and following a DASH diet had a major reduction in systolic BP values of approximately 15 mmHg, as compared with a reduction of 3 mmHg in the control group.[19] Importantly, with such BP reductions, more than half of the patients in the intervention group reached the

recommended goals for daytime ambulatory BP monitoring.[19] BP reductions with a combination of lifestyle factors were discussed in previous studies on hypertensive patients, but there was no reference to the use of anti-hypertensive medications. A systematic review of randomized controlled trials on patients with elevated blood pressure, reported that a combination of interventions including weight loss, diet and physical activity, had the most marked and significant BP reductions compared to individual modifications (5.5 mmHg compared to 5.0 mmHg for improved diet, 4.6 mmHg for exercise and 3.5 mmHg for alcohol restriction).[23] Similarly, Bacon et al. reported that in subjects with mild hypertension a combined exercise and weight-loss intervention reduced SBP and DBP by 12.5 and 7.9mm Hg, respectively, that was determined to be similar to drug therapy.[24] Our study reports the magnitude of the effect of a combination of unhealthy behavior and uncontrolled hypertension; This association persisted even after adjusting for socioeconomic and cardiovascular risk factors, indicating that a combination of unhealthy behavior is strongly associated with uncontrolled hypertension irrespective of the presence of other risk factors.

Our study also pointed out gender differences as to these associations. Few observational studies evaluated the determinants of uncontrolled hypertension using a gender stratified analysis[9,25] and they were not particularly on unhealthy behaviors. Discrepancy between sexes could be explained by differences in lifestyle habits between men and women as well as to the influence of other confounding factors[6-8] such as other socioeconomic factors (employment, marital status), other diseases (chronic kidney disease) other behavioral factors (such as salt intake and stress) and adherence to anti-hypertensive medications. In addition, some data suggest that sex-related characteristics such as the level of sex hormones may influence the results.[26] Although further research is needed to clarify this difference, nevertheless adopting a global healthy lifestyle is important for prevention of cardiovascular diseases and should be encouraged in the general population.[14]

Lastly, age-and-gender-adjusted results found current smoking to be associated with decreased prevalence of uncontrolled hypertension. Epidemiological studies describe discrepancy with regards to effect of smoking on uncontrolled BP; some studies reported smoking to negatively influence BP control,[27,28] while others found no association[9,25,29] and showed that office BP is not lowered by smoking cessation.[30] Further research can help yield more conclusive results. Nevertheless, smoking is an unhealthy behavior and a major

risk of CVD and cancer; smoking cessation recommendations should be provided to all hypertensive individuals for the prevention of CVD including stroke, myocardial infarction and peripheral artery disease.[1,2,14]

The main strength of our study is the design of CONSTANCES, which ensure sufficient power; we adopted a population-based approach using a large nationwide randomly selected sample of participants. In addition, we used standardized protocols to collect anthropometric data including BP measurements. Furthermore, data were collected through different reliable methods, using national databases and validated questionnaires and there was a lack of missing data. Another major strength of our study is the exploration of the combined effect of unhealthy behaviors and performing an analysis stratified by sex. On the other hand, our study had some limitations. Given the cross-sectional design of the study, it may be difficult to ascertain the temporal order of unhealthy behaviors and uncontrolled hypertension. Also, lifestyle behaviors were self-reported using self-administered questionnaires introducing the possibility of misclassification bias. Our study may be susceptible to selection bias, due to the selection effect associated with voluntary participation, also because CONSTANCES covers only salaried workers excluding agricultural and self-employed workers, therefore the population may not be representative of the general population and the frequency of uncontrolled hypertension and of unhealthy behaviors may be affected. However, all patients in the CONSTANCES study were enrolled through the same procedure and data collection was similar to all, so we can assume that the error was not differential and was unlikely to have biased the estimation of the associations between unhealthy behaviors and uncontrolled hypertension. Moreover, the time frame between recent medication adjustment and BP measurement was not taken into consideration. In fact, antihypertensive medication is a confounding factor in BP measurements, with epidemiologic data on BP often compromised by the effects of antihypertensive medications[31], and certainly recent changes. Nevertheless, this is common in epidemiologic studies of cross-sectional design; prospective data from CONSTANCES can help in considering this point. Lastly, excessive salt intake is considered an unhealthy behavior, but we weren't able to study its effect on uncontrolled hypertension because quantitative data on salt intake are not available since dietary habits were evaluated using a non-quantitative food frequency questionnaire.

In conclusion, this study provides further evidence of the association between unhealthy behaviors and uncontrolled hypertension, on an individual and combined level.

An unhealthy lifestyle, characterized by non-adherence to dietary recommendations, overweight or obesity and heavy alcohol consumption, is associated with greater odds of uncontrolled hypertension, which increased with increased number of unhealthy behaviors. Our findings revealed that the associations were significant in men only, suggesting the presence of other factors influencing uncontrolled hypertension. Although further research is needed to clarify the reasons behind the gender-based differences, our findings contribute to epidemiologic data of utmost importance in the management of hypertension, especially in the presence of limited data on the effect of lifestyle factors on hypertension control. From a population-based perspective, our study advocates that public health strategies should promote improvement of modifiable behaviors through a multidisciplinary lifestyle changes approach, which could offer considerable benefits in the treatment and control of hypertension, particularly in men.

METHODS

Study design and study population

Details concerning objectives and study design of the cohort CONSTANCES (http://www.constances.fr/index_EN.php) have been previously published.[15,32] Briefly, CONSTANCES is a prospective epidemiological cohort composed of randomly selected adult participants aged 18-69 years at inception affiliated with the French National Health Insurance Fund database (CNAM; General scheme which covers 85% of the general French population) following a sampling scheme stratified on age, gender, socioeconomic status and region of France.

Volunteers who agreed to participate in the study had to fill self-administered questionnaires and were invited to attend to one of the 22 selected health-screening centers (HSCs) to benefit from a comprehensive health examination. They were also linked through national social and health administrative databases. Through these different sources, social, demographic, health, behavioral, occupational, biological, and anthropometric data were collected. All the participants included in the CONSTANCES cohort have signed an informed consent form. This research follows the tenets of the Declaration of Helsinki and was approved by the National Data Protection Authority (*Commission Nationale Informatique et Libertés*; CNIL) and the Institutional Review Board of the National Institute for Medical Research and the local Committee for Persons Protection (*Comité de Protection des Personnes*).

Between February 2012 and January 2018, a total of 87,808 volunteer participants were recruited and linked to the French health insurance administrative database.

Study participants

The present study is a cross-sectional analysis on participants who were known to have hypertension recorded by the physician or measured during the medical examination at the HSC and receiving antihypertensive medications. A total of 10,764 subjects were eligible to be included, of which we excluded 54 participants with low body mass index (BMI <18kg/m^2). We therefore analyzed 10,710 hypertensive treated participants.

Uncontrolled blood pressure

BP measurements were taken during the clinical examination at the HSC based on standardized operational procedures (SOPs).[33] Systolic BP and diastolic BP were measured in each arm at 2 minutes interval after 5 minutes of rest and using an automated oscillometric sphygmomanometer. The arm giving the highest systolic BP was considered the reference arm and a third BP measure was taken after 1 minute of rest, the average of these 2 measurements was considered. Uncontrolled BP was defined as mean systolic BP ≥140 mm Hg and/or mean diastolic BP ≥90 mm Hg.[34]

Behavioral risk factors definitions

Lifestyle behavior was assessed through validated self-administered questionnaires.

Alcohol consumption was determined considering the quantity and type of alcoholic beverages consumed the previous week.[35] We subsequently defined alcohol consumption as never/light (0–3 glass/week (0–30 g/week) for men and 0–2 (0–20 g/week) for women), moderate (4–21 (40–210 g/week) glass/week for men and 3–14 (30–140 g/week) for women) and heavy drinkers (>21 glass/week (>210 g/week) for men and >14 (>140 g/week) for women).[36] Heavy drinking was considered an unhealthy behavior.

Physical activity was assessed through three questions that considered the frequency of transferring, leisure time activity and sports.[37] We assigned 0, 1, or 2 points for each question based on an escalating frequency of activity, then a score of 0-6 was calculated and physical activity level was classified as sedentary (0-2), moderately active (3-4) and highly active (5-6). Sedentary level was considered an unhealthy behavior.[37]

Dietary assessment was done through a validated 52-items food frequency questionnaire (FFQ) from which a DASH score was constructed based on 8 food groups or nutrients for which consumption should be increased (fruits, vegetables, nuts and legumes, low-fat dairy, whole grains) or reduced (sodium, sweetened beverages, red and processed

meats).[38] Consumption of each dietary component was divided into quintiles, and participants' intakes were assigned 1-5 points according to a gender-specific intake ranking.[38,39] Component scores were summed, and an overall DASH score ranging from 8-40 was calculated. The DASH score was subsequently collapsed to tertiles for analysis; a higher tertile indicating a higher dietary quality, adherence to dietary recommendations was subsequently categorized into low, medium and high. We considered low/medium dietary adherence an unhealthy behavior.

Body mass index (BMI, kg/m2) was calculated at the HSC, then categorized into three classes: normal (≤25 kg/m2), overweight (25 kg/m2< BMI <30 kg/m2), and obese (≥30 kg/m2). We considered overweight/obese (BMI >25 kg/m2) an unhealthy behavior. Accordingly, participants could exhibit 0 (none), 1, 2, 3, or 4 unhealthy behaviors.

Covariates

Education level was collected according to the International Standard Classification of Education (ISCED)[40] and was then classified into three levels: High school diploma or less (≤13 years of education), undergraduate degree (14–16 years of education) and postgraduate degree (≥17 years of education). Marital status was categorized into couple life or single (including widowed or separated/divorced). Household monthly income was categorized into: <1000; 1000-2099; 2100-4199; ≥ 4200 euros per month.

Blood glucose, triglycerides and total cholesterol were measured by taking fasting blood samples at the HSC. Diabetes mellitus status was based on either receiving anti-diabetic medication or a fasting blood glucose concentration greater than or equal to 7mmol/L. Dyslipidemia was defined as having a fasting plasma total-cholesterol or triglycerides level of ≥6.61 mmol/L (255 mg/dL) or >1.7 mmol/L (150 mg/dL) respectively. History of CV diseases was considered as any self-reported previous diagnosis of angina pectoris, myocardial infarction, cerebrovascular accident or peripheral artery disease.[14] Chronic kidney disease was defined as known proteinuria or decreased renal function (creatinine clearance<60ml/min calculated by the Cockroft-Gault equation) for more than 3 months[24], or a chronic kidney disease diagnosed by biopsy or renal ultrasound and confirmed by a nephrologist.

Statistical analysis

Descriptive analysis was performed using counts and percentages or mean ± standard deviation (SD). Each characteristic was compared between subjects with controlled and uncontrolled hypertension using logistic regressions adjusted for age and sex. In addition, we compared characteristics of subjects according to the number of unhealthy behaviors using logistic regressions adjusted for age and stratified by sex. Also with logistic models, we estimated the association between uncontrolled hypertension and unhealthy behaviors. In a first step, models were adjusted for age, education and monthly income (Model 1). In a second step, models were further adjusted for diabetes and dyslipidemia (Model 2). We first performed separate models for each unhealthy behavior using categorical variables and binary variables. Then, we examined the association between uncontrolled hypertension and the number of unhealthy behaviors (0-≥3) independently associated with control of hypertension. Adjusted odds ratios (ORa) were presented along with 95% confidence interval (CI), all statistical analyses were performed with SAS 9.4 (SAS Institute) and $p \leq 0.05$ was considered significant.

Data availability

The datasets generated during and/or analyzed during the current study are available from the CONSTANCES principal investigator (marie.zins@inserm.fr) provided that the procedures described in the CONSTANCES Charter (http://www.constances.fr/charter) are fulfilled.

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Authors' contributions:

MZ and MG obtained funding for the CONSTANCES study cohort and conducted the CONSTANCES study. MC, AV, and JB developed the research question. MC, AV, JB and PS contributed to the study design and analysis plan. SK and MZ acquired the data. AV performed the statistical analyses. MC drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Additional information

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and all authors declare no competing interests.

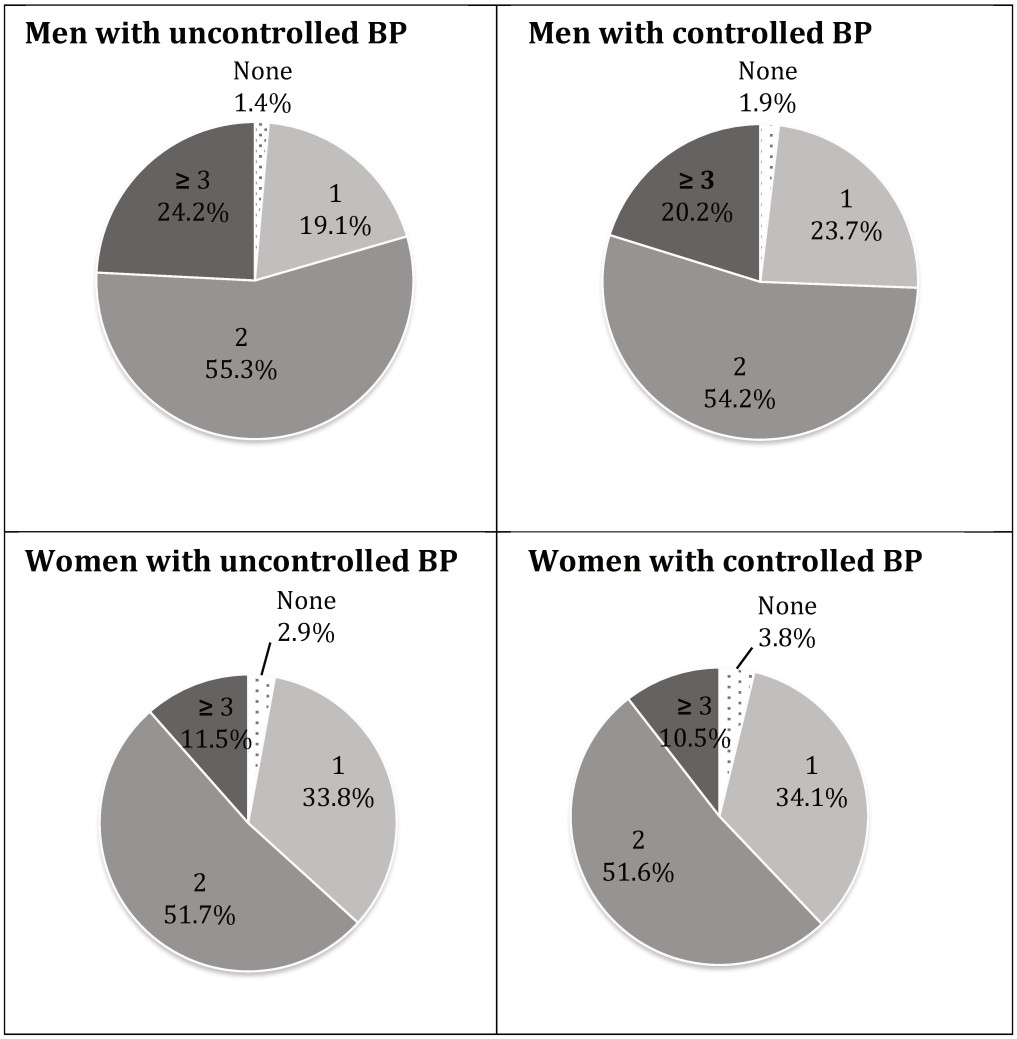

Figure 1. Proportion of subjects by number of unhealthy behaviors stratified by sex

Table 1. Frequency of uncontrolled hypertension according to characteristics of participants

Characteristic	*All participants n, (%)*	*Uncontrolled hypertension n, (%)*	*Controlled hypertension n, (%)*	*P value*
Overall	**10710 (100)**	**6003 (56.1)**	**4707 (43.9)**	
Gender				
Male	6032 (56.3)	3776 (62.9)	2256 (47.9)	<0.001
Female	4678 (43.7)	2227 (37.1)	2451 (52.1)	
Age, year, mean	59.8±8.6	61.0±7.7	58.2±9.3	<0.001
Age, year				<0.001
[18-39]	342 (3.2)	107 (1.8)	235 (5.0)	
[40-49]	1064 (9.9)	471 (7.8)	593 (12.6)	
[50-59]	3053 (28.5)	1596 (26.6)	1457 (30.9)	
≥60	6251 (58.4)	3829 (63.8)	2422 (51.5)	
Systolic BP, mmHg	142.6±17.4	154.4±12.7	127.5±8.7	<0.001
Diastolic BP, mmHg	81.8±9.9	86.7±9.0	75.6±7.2	<0.001
Heart rate, beats per min	65±11	66±12	65±11	<0.001
Serum creatinine (mmol/l)	78.3±21.5	78.9±19.9	77.4±23.3	0.001
Education level				<0.001
≤ high school diploma	4754 (44.4)	2812 (46.8)	1942 (41.3)	
Undergraduate degree	1693 (15.8)	947 (15.8)	746 (15.8)	
Postgraduate degree	4263 (39.8)	2244 (37.4)	2019 (42.9)	
Income of the house/month				0.615
Less than 1000 €	504 (4.7)	269 (4.5)	235 (5.0)	
1000 – 2099 €	2287 (21.3)	1279 (21.3)	1008 (21.4)	
2100 – 4199 €	5201 (48.6)	2935 (48.9)	2266 (48.1)	
More or equal than 4200 €	2718 (25.4)	1520 (25.3)	1198 (25.5)	
Familial situation				<0.001
Single	2554 (23.8)	1319 (22.0)	1235 (26.2)	
Couple life	8156 (76.2)	4684 (78.0)	3472 (73.8)	
Oral contraceptive or HRT*	958 (20.5)*	434 (19.5)*	524 (21.4)*	0.0580
BMI (Kg/m^2)	28.1±5.0	28.3±4.9	27.7±5.0	<0.001
BMI class				<0.001
< 25	3101 (29.0)	1568 (26.1)	1533 (32.6)	
25.0-29.9	4364 (40.7)	2529 (42.1)	1835 (39.0)	
≥30.0	3245 (30.3)	1906 (31.8)	1339 (28.4)	
Physical activity				0.008
Sedentary	1095 (10.2)	586 (9.8)	509 (10.8)	
Moderate	3928 (36.7)	2152 (35.8)	1776 (37.7)	
High	5687 (53.1)	3265 (54.4)	2422 (51.5)	
DASH score	26.1±3.7	26.0±3.7	26.3±3.7	<0.001
DASH categories				<0.001
Low	1361 (12.7)	750 (12.5)	611 (13.0)	

Medium	8413 (78.6)	4766 (79.4)	3647 (77.5)	
High	936 (8.7)	487 (8.1)	449 (9.5)	
Alcohol consumption				<0.001
Never/light	1828 (17.1)	931 (15.5)	897 (19.1)	
Moderate	7271 (67.9)	4053 (67.5)	3218 (68.4)	
Heavy	1611 (15.0)	1019 (17.0)	592 (12.6)	
Smoking status				<0.001
Non-smoker	4987 (46.6)	2740 (45.6)	2247 (47.7)	
Current smoker	1200 (11.2)	584 (9.7)	616 (13.1)	
Ex-smoker	4523 (42.2)	2679 (44.7)	1844 (39.2)	
History of CV events	1401 (13.1)	709 (11.8)	692 (14.7)	<0.001
Diabetes	1661 (15.5)	1045 (17.4)	616 (13.1)	<0.001
Dyslipidemia	6418 (59.9)	3733 (62.2)	2685 (57.0)	<0.001
Chronic kidney disease	176 (1.7)	99 (1.6)	78 (1.7)	0.345
Anti-hypertensive medications				0.001
Mono-therapy	5932 (56.3)	3227 (54.6)	2705 (58.4)	
Dual therapy	3619 (34.3)	2081 (35.2)	1538 (33.2)	
Triple therapy or more	995 (9.4)	603 (10.2)	392 (8.4)	

Data are mean$\pm$SD for quantitative variables or percent for categorical.
P from logistic regression model adjusted for age and sex.
***** Frequency among women only
Abbreviations: BMI, body mass index (Kg/m^2); BP, blood pressure; CV, cardiovascular; DASH, dietary approach to stop hypertension; HRT, hormone replacement therapy; SD, standard deviation.

Table 2. Men's characteristics according to the number of unhealthy behaviors

Number of unhealthy behaviors	0	1	2	3 or more	P value
Overall, n (%)	**97 (1.6)**	**1255 (20.8)**	**3312 (54.9)**	**1368 (22.7)**	-
Age, year, mean	60.9±8.6	60.1±8.9	60.2±8.1	60.1±7.9	0.767
Age, year					0.003
[18-39]	3 (3.1)	52 (4.1)	78 (2.4)	24 (1.8)	
[40-49]	7 (7.2)	106 (8.5)	312 (9.4)	134 (9.8)	
[50-59]	22 (22.7)	329 (26.2)	947 (28.6)	420 (30.7)	
≥60	65 (67.0)	768 (61.2)	1975 (59.6)	790 (57.7)	
Systolic BP	144.6±17.8	143.5±17.3	145.3±16.5	146.0±16.2	0.001
Diastolic BP	81.9±10.0	81.8±9.6	83.6±9.8	84.2±9.8	<0.001
Uncontrolled BP	53 (54.6)	721 (57.5)	2089 (63.1)	913 (66.7)	<0.001
Heart rate, beats per min	59±9	62±11	65±11	67±12	<0.001
Serum creatinine (mmol/l)	87.4±35.3	85.3±20.9	86.6±22.3	85.3±23.4	0.184
Education level					<0.001
≤ high school diploma	33 (34.0)	462 (36.8)	1573 (47.5)	661 (48.3)	
Undergraduate degree	11 (11.3)	192 (15.3)	472 (14.3)	190 (13.9)	
Postgraduate degree	53 (54.6)	601 (47.9)	1267 (38.2)	517 (37.8)	
Income of the house/month					<0.001
Less than 1000 €	6 (6.2)	48 (3.8)	116 (3.5)	89 (6.5)	
1000 – 2099 €	16 (16.5)	195 (15.5)	635 (19.2)	304 (22.2)	
2100 – 4199 €	41 (42.3)	564 (45.0)	1670 (50.4)	597 (43.7)	
More or equal than 4200 €	34 (35.0)	448 (35.7)	891 (26.9)	378 (27.6)	
Familial situation					0.001
Single	22 (22.7)	228 (18.2)	595 (18.0)	314 (22.9)	
Couple life	75 (77.3)	1027 (81.8)	2717 (82.0)	1054 (77.1)	
BMI (Kg/m^2)	23.2±1.4	24.7±3.4	29.2±3.9	30.1±4.0	<0.001
BMI class					<0.001
< 25	97 (100)	965 (76.9)	250 (7.5)	27 (2.0)	
25.0-29.9	0 (0)	198 (15.8)	1904 (57.5)	752 (55.0)	
≥30.0	0 (0)	92 (7.3)	1158 (35.0)	589 (43.0)	
Physical activity					<0.001
Sedentary	0 (0)	2 (0.2)	115 (3.5)	553 (40.4)	
Moderate	28 (28.9)	450 (35.9)	1407 (42.5)	352 (25.7)	
High	69 (71.1)	803 (64.0)	1790 (54.0)	463 (33.9)	
DASH score	32.1±1.8	27.1±3.7	25.1±3.3	23.8±3.4	<0.001
DASH categories					<0.001
Low	0 (0)	72 (5.7)	408 (12.3)	284 (20.8)	
Medium	0 (0)	879 (70.0)	2829 (85.4)	1079 (78.9)	
High	97 (100)	304 (24.2)	75 (2.3)	5 (0.4)	
Alcohol consumption					<0.001
Never/light	20 (30.6)	174 (13.9)	443 (13.4)	89 (6.5)	
Moderate	77 (79.4)	1069 (85.2)	2659 (80.3)	322 (23.5)	

Heavy	0 (0)	12 (0.9)	210 (6.3)	957 (70.0)	
Smoking status					<0.001
Non-smoker	45 (46.4)	549 (43.7)	1229 (37.1)	389 (28.4)	
Current smoker	13 (13.4)	110 (8.8)	350 (10.6)	225 (16.5)	
Ex-smoker	39 (40.2)	596 (47.5)	1733 (52.3)	754 (55.1)	
History of CV events	20 (20.6)	235 (18.7)	585 (17.7)	259 (18.9)	0.630
Diabetes	9 (9.3)	150 (11.9)	687 (20.7)	322 (23.5)	<0.001
Dyslipidemia	55 (56.7)	686 (54.7)	2225 (67.2)	993 (72.6)	<0.001
Chronic kidney disease	5 (5.2)	21 (1.7)	64 (1.9)	23 (1.7)	0.191
Anti-hypertensive medications					<0.001
Mono-therapy	59 (62.1)	746 (60.2)	1660 (50.8)	638 (47.2)	
Dual therapy	25 (26.3)	408 (32.9)	1247 (38.2)	531 (39.3)	
Triple therapy or more	11 (11.6)	85 (6.9)	362 (11.0)	183 (13.5)	

Data are mean$\pm$SD for quantitative variables or percent for categorical.
P from logistic regression model adjusted for age.
Abbreviations: BMI, body mass index (Kg/m^2); BP, blood pressure; CV, cardiovascular; DASH, dietary approach to stop hypertension; SD, standard deviation.

Table 3. Women's characteristics according to the number of unhealthy behaviors

Number of unhealthy behaviors	0	1	2	3 or more	P value
Overall, n(%)	**157 (3.4)**	**1590 (34.0)**	**2416 (51.6)**	**515 (11.0)**	-
Age, year, mean	60.2±9.2	59.2±9.2	59.3±8.8	59.4±8.8	0.595
Age, year					0.476
[18-39]	6 (3.8)	72 (4.5)	92 (3.8)	15 (2.9)	
[40-49]	11 (7.0)	170 (10.7)	265 (11.0)	59 (11.5)	
[50-59]	50 (31.9)	429 (27.0)	705 (29.2)	151 (29.3)	
≥60	90 (57.3)	919 (57.8)	1354 (56.0)	290 (56.3)	
Systolic BP	138.1±17.9	138.8±18.6	139.6±17.4	140.2±16.9	0.271
Diastolic BP	77.0±9.0	78.9±10.1	80.4±9.6	81.3±9.5	<0.001
Uncontrolled BP	65 (41.4)	753 (47.4)	1152 (47.7)	257 (49.9)	0.312
Heart rate, beats per min	64±9	65±10	67±11	68±11	<0.001
Serum creatinine (mmol/l)	68.1±14.4	68.0±13.2	68.9±10.5	68.3±10.9	0.675
Education level					<0.001
≤ high school diploma	44 (28.0)	581 (36.5)	1162 (48.1)	238 (46.2)	
Undergraduate degree	32 (20.4)	292 (18.4)	422 (17.5)	82 (15.9)	
Postgraduate degree	81 (51.6)	717 (45.1)	832 (34.4)	195 (37.9)	
Income of the house/month					<0.001
Less than 1000 €	7 (4.5)	67 (4.2)	125 (5.2)	46 (8.9)	
1000 – 2099 €	26 (16.5)	332 (20.9)	656 (27.2)	123 (23.9)	
2100 – 4199 €	75 (47.8)	804 (50.6)	1209 (50.0)	241 (46.8)	
More or equal than 4200 €	49 (31.2)	387 (24.3)	426 (17.6)	105 (20.4)	
Familial situation					<0.001
Single	69 (44.0)	449 (28.2)	709 (29.4)	168 (32.6)	
Couple life	88 (56.0)	1141 (71.8)	1707 (70.6)	347 (67.4)	
Oral contraceptive or HRT	36 (22.9)	392 (24.4)	449 (18.4)	81 (14.4)	<0.001
BMI (Kg/m^2)	22.2±1.7	23.7±3.6	29.9±5.2	31.0±5.2	<0.001
BMI class					<0.001
< 25	157 (100)	1337 (84.1)	261 (10.8)	7 (1.4)	
25.0-29.9	0 (0)	134 (8.4)	1117 (46.2)	259 (50.3)	
≥30.0	0 (0)	119 (7.5)	1038 (43.0)	249 (48.3)	
Physical activity					<0.001
Sedentary	0 (0)	6 (0.4)	127 (5.3)	292 (56.7)	
Moderate	48 (30.6)	516 (32.4)	1023 (42.3)	104 (20.2)	
High	109 (69.4)	1068 (67.2)	1266 (52.4)	119 (23.1)	
DASH score	32.9±1.7	27.9±3.5	26.6±3.1	25.8±3.4	<0.001
DASH categories					<0.001
Low	0 (0)	151 (9.5)	337 (14.0)	109 (21.2)	
Medium	0 (0)	1173 (73.8)	2047 (84.7)	406 (78.8)	
High	157 (100)	266 (16.7)	32 (1.3)	0 (0)	
Alcohol consumption					<0.001

Never/light	45 (28.7)	349 (22.0)	611 (25.3)	97 (18.8)	
Moderate	112 (71.3)	1234 (77.6)	1639 (67.8)	159 (30.9)	
Heavy	0 (0)	7 (0.4)	166 (6.9)	259 (50.3)	
Smoking status					0.009
Non-smoker	99 (63.1)	901 (56.7)	1500 (62.1)	275 (53.4)	
Current smoker	15 (9.5)	197 (12.4)	224 (9.3)	66 (12.8)	
Ex-smoker	43 (27.4)	492 (30.9)	692 (28.6)	174 (33.8)	
History of CV events	4 (2.6)	108 (6.8)	157 (6.5)	33 (6.4)	0.145
Diabetes	6 (3.8)	68 (4.3)	327 (13.5)	92 (17.9)	<0.001
Dyslipidemia	72 (45.9)	705 (44.3)	1371 (56.8)	311 (60.4)	<0.001
Chronic kidney disease	5 (3.2)	23 (1.5)	28 (1.2)	7 (1.4)	0.229
Anti-hypertensive medications					<0.001
Mono-therapy	107 (68.6)	1052 (67.7)	1383 (58.3)	287 (56.4)	
Dual therapy	46 (29.5)	410 (28.4)	785 (33.1)	167 (32.8)	
Triple therapy or more	3 (1.9)	92 (5.9)	204 (8.6)	55 (10.8)	

Data are mean$\pm$SD for quantitative variables or percent for categorical.
P from logistic regression model adjusted for age.
Abbreviations: BMI, body mass index (Kg/m^2); BP, blood pressure; CV, cardiovascular; DASH, dietary approach to stop hypertension; HRT, hormone replacement therapy; SD, standard deviation.

Table 4. Association between uncontrolled hypertension and the number of unhealthy behaviors in men

Term	*Model 1*	*P value*	*Model 2*	*P value*
DASH		**0.019**		**0.017**
High	1.00 (ref)	-	1.00 (ref)	-
Medium	1.26 [1.04-1.52]	0.020	1.26 [1.04-1.53]	0.018
Low	1.41 [1.11-1.79]	0.005	1.41 [1.11-1.79]	0.004
Low/medium vs. high	1.13 [0.97-1.34]	0.113	1.14 [0.97-1.35]	0.105
Physical activity		**0.041**		**0.031**
High	1.00 (ref)	-	1.00 (ref)	-
Moderate	0.86 [0.77-0.97]	0.012	0.86 [0.77-0.96]	0.009
Sedentary	0.91 [0.76-1.08]	0.285	0.90 [0.76-1.08]	0.274
Moderate/sedentary vs. high	0.87 [0.78-0.98]	0.013	0.87 [0.78-0.97]	0.010
BMI		**<0.001**		**<0.001**
<25	1.00 (ref)	-	1.00 (ref)	-
25.0-29.9	1.23 [1.07-1.40]	0.002	1.25 [1.09-1.43]	0.001
≥30.0	1.54 [1.33-1.79]	<0.001	1.57 [1.35-1.83]	<0.001
≥25 vs. <25	1.33 [1.18-1.51]	<0.001	1.35 [1.19-1.53]	<0.001
Alcohol consumption		**0.003**		**0.003**
Never/light	1.00 (ref)	-	1.00 (ref)	-
Moderate	1.07 [0.91-1.27]	0.410	1.08 [0.91-1.27]	0.367
Heavy	1.33 [1.09-1.61]	0.004	1.34 [1.10-1.63]	0.003
Heavy vs. moderate/never	1.25 [1.09-1.44]	0.001	1.25 [1.09-1.44]	0.001
Nb. of unhealthy behaviors		**<0.001**		**<0.001**
0	1.00 (ref)	-	1.00 (ref)	-
1	1.12 [0.74-1.71]	0.585	1.11 [0.73-1.69]	0.612
2	1.39 [0.92-2.09]	0.120	1.38 [0.91-2.08]	0.123
3 or more	1.66 [1.08-2.52]	0.019	1.67 [1.09-2.53]	0.018

Abbreviations: BMI, body mass index (Kg/m^2); DASH, dietary approach to stop hypertension
Model 1: logistic regression model adjusted for age, education level, monthly income.
Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, and dyslipidemia.

Article 4 (Submitted)

Title: Predictors of uncontrolled blood pressure in hypertensive treated individuals – The CONSTANCES population based study

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Abstract:

Background: Uncontrolled hypertension is common among treated hypertensive individuals and contributes significantly to increased risk of cardiovascular disease. Factors influencing blood pressure (BP) control are important to be identified.

Objectives: We aimed to assess sociodemographic, clinical and behavioral factors associated with uncontrolled BP among treated hypertensive individuals.

Methods: We conducted cross-sectional analysis using data from the population based cohort study CONSTANCES. We included 10,710 participants previously diagnosed with hypertension and taking antihypertensive medications. Uncontrolled BP was defined as mean systolic BP ≥140 mm Hg and/or mean diastolic BP ≥90 mm Hg. Data were collected through self-administered questionnaires, clinical health examination and link with national social and health administrative databases. Gender specific age-adjusted multivariable analyses were performed using logistic regression models.

Results: The prevalence of uncontrolled BP was 56% and it was higher in men than in

women (ORa 1.80, 95% CI 1.67 –1.94). A breakdown of uncontrolled BP found that 61.6%, 5.1% and 33.3% had uncontrolled only systolic BP, only diastolic BP and both components, respectively. In both sexes, low level of education was positively and history of cardiovascular events was negatively associated with uncontrolled BP. In men additional predictors included living in couple (ORa 1.22, 95% CI 1.04–1.42), overweight and obesity (ORa 1.20, 95% CI 1.04 –1.42 and ORa 1.49, 95%CI 1.28-1.75, respectively), low and medium adherence to DASH-diet (ORa 1.39, 95%CI 1.02-1.65 and ORa 1.19, 95% CI 1.03–1.38, respectively), heavy alcohol consumption (ORa 1.26, 95% CI 1.03–1.54) and physical inactivity ($p<0.008$). In women, dyslipidemia (ORa 0.87, 95% CI 0.77-0.98) and smoking (ORa 0.69 95% CI 0.56-0.85) were associated with decreased odds of uncontrolled BP.

Conclusion: From a population-based perspective, socioeconomic and behavioral characteristics were predictors of uncontrolled HTN. Modifiable risk factors such as weight, diet, and alcohol use influence BP control.

Keywords: epidemiology, risk factors, uncontrolled hypertension, lifestyle behavior, socioeconomic status

INTRODUCTION

Arterial hypertension is a global public health issue affecting more than 1 billion individuals worldwide and causing an estimated ten million deaths every year [1]. Uncontrolled hypertension contributes significantly to increased risk of cardiovascular disease, stroke and chronic kidney disease [2]. The importance of BP reduction and control was highlighted in a meta-analysis showing that a 10mmHg reduction in systolic BP reduces the risk of major cardiovascular events by 20%, stroke by 27% and all-cause mortality by 13% [3]. Despite the availability of efficient and well-tolerated medications, widespread public health efforts to treat individuals with hypertension and periodic publication of guidelines for the management of hypertension, low BP control rates at the 140/90mmHg threshold have been frequently reported among treated hypertensive individuals. In the United States, data analysis from the National Health and Nutrition Examination Survey (NHANES) found that among treated individuals around 45% had uncontrolled BP [4]. Within Europe, BP control rate among hypertensive individuals reached 36% in England [5], 40% in Portugal [6] and 51% in Germany [7]. Similarly to these countries the estimated prevalence of hypertension in France is 31% and 50.4% of hypertensive treated patients are not controlled [8].

A broad range of factors have been identified that contribute to poor BP control. These include, physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled) [9], deficiencies of healthcare systems in their global approach to chronic diseases [10] and low adherence to treatment including antihypertensive prescriptions and lifestyle changes [11]. In addition, factors such as socio-economic characteristics and poor lifestyle behaviors have been described as predictors of poor BP control [12]. Studies suggest that unhealthy lifestyle behaviors including heavy alcohol drinking, lack of physical activity, poor dietary habits, overweight and stress may contribute to inadequate BP control [12,13].

In France, efforts to improve BP control have been made. For example one of the objectives of the French Nutrition and Health Program launched in 2001 by the French Ministry of Health was to prevent high BP through nutrition [14]. In addition the French League Against Hypertension and the French Society of Hypertension, have suggested a simplified decisional algorithm that consist of 7 key points aimed to improve BP control and to achieve over 70% blood pressure control in treated hypertensive patients by 2015 [15]. However, updated epidemiological data have not been published yet, and there's a lack of studies

evaluating factors associated with poor BP control from a large sample of non-institutionalized adult French population. Therefore, we conducted this study to assess sociodemographic, clinical and behavioral predictors of uncontrolled BP among treated hypertensive individuals from the CONSTANCES cohort French study.

METHODS

Study design and study population

The CONSTANCES cohort is an ongoing prospective study designed as a national research infrastructure and intended to contribute to the development of epidemiologic research (http://www.constances.fr/index_EN.php). Details concerning study protocol, design, and methods have been previously published [16, 17]. Briefly, adults aged 18-69 years at inception were randomly selected from the French National Health Insurance Fund database (CNAM; Caisse nationale d'assurance maladie des travailleurs salariés), that covers about 85% of the French general population. Those who agreed to participate in the study had to sign an informed consent and to complete self-administered questionnaires gathering social, demographic, health and lifestyle behavior characteristics. They were also invited to go to one of the twenty-two participating Health Screening Centers (HSC) throughout France to benefit from a comprehensive health examination whereby medical, paraclinic exams and blood tests were performed. Through national health and social databases, detailed information concerning occupational status as well as health events and medical acts (medication, hospitalization…) were collected. The National Data Protection Authority and the Institutional Review Board of the National Institute for Medical Research and the local Committee for Persons Protection approved the CONSTANCES study

The present ancillary study is a cross-sectional analysis on volunteer participants from the CONSTANCES study who were recruited between February 2012 and January 2018 and were linked to the French health insurance administrative database. Eligible population included participants who had been diagnosed with hypertension and were taking antihypertensive medications and for whom BP measurements were available. The sample size consisted of 10,710 participants.

Anthropometrics and blood pressure measurements

Anthropometrics and blood pressure measurements were taken during the clinical examination at the HSC based on standardized operational procedures (SOPs) [18]. SBP and

DBP were measured in each arm at 2 minutes interval in a supine position after 5 minutes of rest and using an automated oscillometric sphygmomanometer. A third measure was taken on the arm giving the highest SBP value (reference arm) after 1 minute of further rest. The average of the reference arm measurement and the third measurement was considered.

Creatinine, blood glucose, triglycerides, total and HDL cholesterol were measured by taking fasting blood samples. Weight and height were measured respectively with a scale and a measuring rod without shoes. Body mass index (BMI) was calculated and was categorized into three classes: normal weight (BMI ≤25 kg/m2), overweight (25 kg/m2< BMI <30 kg/m2), and obese (BMI ≥30 kg/m2).

BP control and diseases definitions

Uncontrolled BP was defined as mean SBP ≥140 mmHg and/or mean DBP ≥90 mmHg [19]. Diabetes mellitus status was based on either self-reported type II diabetes, receiving anti-diabetic medication or a fasting blood glucose concentration greater than or equal to 7mmol/L. Dyslipidemia was defined as having a fasting plasma total-cholesterol or triglycerides level of ≥6.61 mmol/L (255 mg/dL) or >1.7 mmol/L (150 mg/dL) respectively. History of CV diseases was considered as any self-reported previous diagnosis of angina pectoris, myocardial infarction, cerebrovascular accident or peripheral artery disease. Chronic kidney disease was defined as known proteinuria or decreased renal function (creatinine clearance<60ml/min calculated by the Cockroft-Gault equation) for more than 3 months [20], or a chronic kidney disease diagnosed by biopsy or renal ultrasound and confirmed by a nephrologist.

Socioeconomic status

Education level was collected according to the International Standard Classification of Education (ISCED) [21] and was then classified into three levels: High school diploma or less (≤ 13 years of education), undergraduate degree (14–16 years of education) and postgraduate degree (≥17 years of education). Marital status was categorized into couple life or single (including widowed or separated/divorced). Household monthly income was categorized into: <1000; 1000-2099; 2100-4199; ≥ 4200 euros per month.

Behavioral risk factors definitions

Lifestyle behavior was assessed through self-administered questionnaires.

Smoking status was reported as non-smoker, former smoker or current smoker. Alcohol consumption was defined as never/light (0–30 g/week for men and 0–20 g/week for women), moderate (40–210 g/week for men and 30–140 g/week for women) and heavy drinkers (>210 g/week for men and >140 g/week for women) [22]. Physical activity (PA) was assessed through three questions that considered the frequency of transferring, leisure time activity and sports. We assigned 0, 1, or 2 points for each question based on an escalating frequency of activity [23], then a score of 0-6 was calculated and physical activity level was classified as sedentary (0-2), moderately active (3-4) and highly active (5-6). Dietary assessment was done through a validated 52-items food frequency questionnaire (FFQ) from which a DASH score was constructed based on food groups described by Fung and colleagues and it ranged from 8-40 points [24]. The DASH score was subsequently collapsed to tertiles for analysis; a higher tertile indicating a higher dietary quality, adherence to dietary recommendations was then categorized into low, medium and high.

Statistical analysis

Descriptive analysis was performed for the entire population and for each gender using counts and percentages or mean ± standard deviation (SD). Bivariate analysis was then carried out to compare lifestyle and socioeconomic characteristics in men and women and in individuals with controlled and uncontrolled hypertension, stratified by sex. For categorical variables we used the Pearson's Chi-squared or Fisher's exact tests when applicable. Continuous quantitative variables were analyzed using student (independent) T-test and Mann-Whitney test when normal or abnormal distribution was assumed, respectively. Age adjusted odds ratios (ORa) were calculated along with 95% confidence interval (CI) using logistic regression. Multivariable analysis was performed to assess the association between covariables of interest and uncontrolled hypertension using a backward stepwise likelihood ratio logistic regression for the whole sample and for each gender; ORa with 95%CI were presented. Using the General Linear Model, age-adjusted mean systolic BP was studied across the different categories of selected variables. Valid 2-sided p-values were reported and $p \leq 0.05$ was considered statistically significant. Statistical analyses were done using SAS software (version 9.4; SAS Institute, Carry, NC).

RESULTS

The baseline characteristics of the study population are summarized in table 1. The mean ± SD age of the population was of 59.8± 8.6 and 56.3% were males. The mean ± SD SBP and DBP were 142.6± 17.4 and 81.8± 9.9, respectively.

The prevalence of uncontrolled BP was 56% and it was higher in men than in women (62.6% vs. 47.6% respectively, p<0.0001) (ORa =1.80, 95% CI =1.67 –1.94). A high and a progressively increased proportion of uncontrolled BP was seen across age categories with the highest found in those more than 65 years of age in both sexes (Figure 1). A breakdown of uncontrolled BP by gender is illustrated in figure 2.

Results of the gender stratified univariate analysis, comparing studied factors in controlled and uncontrolled groups are presented in supplementary tables 1 and 2. Among socioeconomic factors and in both sexes, uncontrolled BP was more common in those living in couple and in those with a low education level compared to post-graduate studies. It was also more frequent in men with a lower household monthly income. Regarding lifestyle behaviors, in both men and women, uncontrolled BP was more common in overweight and obese (p<0.001) and in those with increased alcohol consumption and in heavy drinking (ORa 0.66, p<0.001). In men only, a lower mean ± SD DASH score was associated with uncontrolled BP (p=0.0125) and there was an inverse association with physical activity. As to other risk factors, a significant association was seen in those with history of CV events (decreased risk of uncontrolled BP), diabetes or dyslipidemia (in women only).

Results of the multivariable logistic regression analysis, evaluating predictors of uncontrolled BP are presented for men and women in tables 2 and 3, respectively.

Among socioeconomic status variables, living in couple was found to be associated with uncontrolled BP in men only (ORa =1.22, 95% CI =1.04 –1.42; p=0.011), while a moderate (undergraduate) and low (high school diploma) education compared to high education (post-graduate) was found to be positively associated with uncontrolled HTN, in both sexes. As to modifiable risk factors, we found divergent results between men and women; in women there was no association with any of BMI, physical activity, dietary adherence or alcohol consumption, while in men these factors were found to be independently associated with uncontrolled HTN. A gradual increase in the odds of uncontrolled BP was seen in overweight and obese men compared to those with normal BMI (ORa =1.20, 95% CI =1.04 – 1.42 and ORa= 1.49, 95% CI 1.28-1.75, respectively). Similarly, a dose-dependent relationship was seen with dietary adherence, whereby medium and low adherence to

DASH recommendations compared to high adherence was associated with increased odds of uncontrolled HTN (ORa =1.19, 95% CI =1.03 –1.38 and ORa= 1.39, 95% CI 1.02-1.65, respectively). Moreover, heavy alcohol consumption compared to never/light increased the odds of uncontrolled HTN by 1.26-fold (95% CI =1.03 –1.54). Alternatively, there was an inverse relationship with physical activity and smoking status. In men, compared to high-level physical activity, moderate and sedentary levels were negatively associated with uncontrolled hypertension ($p<0.05$). This was also seen in women who currently smoke. Among other studied risk factors, men and women with a history of CV events had respectively, 0.56-fold (95% CI =0.48-0.64) and 0.69-fold (95% CI =0.54-0.89) decrease in the odds of uncontrolled hypertension. Also, women with dyslipidemia were less likely to be associated with uncontrolled BP (ORa =0.87, 95% CI =0.77-0.98). In both sexes, there was no association with either diabetes or chronic kidney disease ($p>0.05$).

DISCUSSION

In this population-based study, half of hypertensive treated individuals had uncontrolled BP and associated predictors differed by gender. Having a history of CV events was negatively associated with uncontrolled hypertension in both sexes. In addition to that, a low education level was positively associated while dyslipidemia and current smoking status were negatively associated with uncontrolled hypertension in women. In men, independent factors associated with uncontrolled BP were: living in couple, having a lower educational level, being overweight or obese, adhering to low or moderate dietary recommendations, consuming alcohol heavily and physical activity (inverse influence).

Prevalence of uncontrolled hypertension

The prevalence of uncontrolled HTN among treated hypertensive individuals reached 56%, which is comparable to the rates reported from two previous national studies composed of a sample representative of the French population. In fact, in 2006 the ENNS study reported that 49.4% of hypertensive treated patients were not controlled [25], while in 2015 the Esteban study described a rate of 50.4% [8]. As such, there was no improvement in the control of HTN from 2006 until 2018, despite new recommendations for the management and control of hypertension [19, 26]. Nevertheless, our results are comparable to the approximate 50% control rate among hypertensive treated individuals reported for high-income countries such as in the United States and Germany [4, 7]. Our

study also shows that almost two out of three had the SBP out of target and 33% had both systolic and diastolic BP uncontrolled; results commonly reported in other studies.

Predictors of uncontrolled hypertension

Socio-demographic factors

Our study found that increased age is associated with increased risk of uncontrolled hypertension that was most frequent in those more than 65 years old. This is consistent with many previous studies [12, 27, 28], arguing that BP control is more challenging due to higher hypertension severity [28] and attributing an increased SBP with increased large artery stiffness [29].

Among the socioeconomic status indices, a lower level of education was significantly and positively associated with uncontrolled HTN in both sexes. Few studies evaluated the influence of socioeconomic determinants on uncontrolled BP and little information is available on the association with level of education. Yet, comparably with our results, one study conducted in Portugal reported a lower education level to be independently associated with uncontrolled BP [30]. The level of education is a crucial socioeconomic measure as it can be reliably recalled and unaffected by later adult health, and was suggested to be the most important socioeconomic factor with an impact on HTN [31]. Lower level of education can justify unhealthy lifestyle habits that could influence behaviors (diet, smoking, exercise and alcohol) [32], increasing the risk of uncontrolled hypertension. As such, maybe more health-education efforts on BP control among treated individuals of lower education level ought to be directed.

Moreover, living in couple was associated with uncontrolled hypertension and was observed in men only. Conflicting results exist in the literature with regards to this association. Yet, our results are consistent with those reported in other studies [27, 33]. Farah el al. aimed to assess, using a gender-stratified approach, the factors contributing to poor SBP, DBP and overall BP control. The study found that in men, being married was associated with overall poor BP control [27]. Likewise, marital status was a predictor of uncontrolled HTN in a study conducted in India [33].

Lifestyle behaviors factors

Among well-described factors, we found BMI, low or medium adherence to DASH dietary pattern and heavy alcohol consumption to be independently associated with uncontrolled hypertension in men only. One randomized controlled trial demonstrated that

a DASH diet combined with increased daily walking promotes clinically relevant reductions in ambulatory BP monitoring (ABPM) in uncontrolled hypertensive patients with type 2 diabetes [34]. More importantly, more than half of these patients reached the recommended goals for daytime ABPM [32]. Similarly, in a sample of hypertensive treated South Koreans, heavy alcohol consumption defined as consumption of more than 60g for men and 40g for women during a single drinking session was determinant of poor BP control at the 140/90 threshold [12].

Surprisingly, we found an inverse relationship with physical activity. Overall, our results contradict results form observational studies that described a strong relationship between physical activity and good BP control [12, 35]. Yet, one study also reported that higher physical activity level ($p = 0.043$) to be associated with uncontrolled hypertension [30]. Our findings could be explained by the fact that we used a less reproducible PA score from the literature and that we did not calculate the corresponding metabolic equivalent (MET) for the type of reported physical activity. Further studies are necessary to assess this aspect.

Likewise, current smoking was associated with decreased odds of uncontrolled hypertension. Epidemiological studies describe discrepancy with regards to effect of smoking on uncontrolled BP; some studies reported smoking to negatively influence BP control [30, 33], while others found no association [12, 27, 35] and showed that office BP is not lowered by smoking cessation [36]. Nevertheless, smoking is an unhealthy behavior and a major risk of CVD and cancer. These findings should not lead to questioning smoking cessation recommendations in all hypertensive individuals for the prevention of CVD including stroke, myocardial infarction and peripheral artery disease [1, 2].

Our study highlighted gender-based predictors of uncontrolled hypertension. This could be attributed to the influence of other confounding variables such the number and type of antihypertensive medications used, adherence to treatment and differences in lifestyle behaviors between men and women. Yet, an unhealthy lifestyle appears to be associated with poor BP control. Therefore, our results suggest that weight management and maintaining a healthy BMI, adherence to nutritional recommendations through the adoption of a DASH-style diet and limitation of alcohol consumption may be associated with lower SBP and can favorably affect BP control in treated hypertensive individuals.

Other risk factors

Of other studied risk factors, individuals with history of CV events and women with dyslipidemia had decreased odds of uncontrolled hypertension.

This has been seen elsewhere, reporting that patients with comorbidities are associated with better BP control [12]. In fact, a previous study found that among patients with hypertension, those with comorbidities were more likely to use health care services than those without comorbidities [37]. Patients who have comorbidities may have been threatened with their comorbid conditions and were more inclined to adhere to treatment regimens and lifestyle modifications than those without comorbidities, resulting in higher rates of BP control in this group.

Study strengths and limitations

The main strength of our study is the design of CONSTANCES, which ensure sufficient power; we adopted a population-based approach using a large nationwide randomly selected sample of participants. In addition, we used standardized protocols to collect anthropometric data including BP measurements. Furthermore, data was collected through different reliable methods, using national databases and validated questionnaires and there was a lack of missing data.

On the other hand, our study had some limitations. Given the cross-sectional design of the study, it may be difficult to ascertain the temporal order of lifestyle behaviors and uncontrolled hypertension. In addition, these variables were self-reported using self-administered questionnaires introducing the possibility of misclassification bias. Moreover, our study may be susceptible to selection bias, due to the selection effect associated with voluntary participation, also because CONSTANCES covers only salaried workers excluding agricultural and self-employed workers. However, all patients in the CONSTANCES study were enrolled through the same procedure and data collection was similar to all, so we can assume that the error was not differential and was unlikely to have biased the estimation of the association between risk factors and uncontrolled hypertension. Lastly we did not take into consideration medication adherence, as the questionnaire did not address this aspect and future prospective data from the CNAM are expected to elaborate this factor and yield more conclusive results.

CONCLUSION

In conclusion, this study provides further epidemiologic data on the burden of uncontrolled hypertension and the apparent challenge in achieving adequate BP control among hypertensive treated individuals. Predictors of uncontrolled HTN included socioeconomic and behavioral characteristics with associations differing by gender. From this population-based perspective, these findings suggest that improvement of modifiable risk factors such as maintaining a normal BMI, adopting of a DASH-style diet, and limiting alcohol consumption could offer an important approach in the treatment of hypertension.

Declaration of conflicting interests:

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions:

MZ and MG obtained funding for the CONSTANCES study cohort and conducted the CONSTANCES study. MC, AV, and JB developed the research question. MC, AV, JB and PS contributed to the study design and analysis plan. SK and MZ acquired the data. AV performed the statistical analyses. MC drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1, Baseline characteristics of the study population

Characteristic	*All*	*Men*	*Women*	*P value*
Number (%)	**10710**	**6032 (56.3)**	**4678 (43.7)**	
Age (years)	59.8±8.6	60.2±8.2	59.3±9.0	<0.001
Duration of Hypertension	9.6±16.4	13.0±18.8	5.3±11.1	<0.001
Systolic BP	142.6 ±17.4	145.1±16.6	139.3±17.8	<0.001
Diastolic BP	81.8 ±9.9	83.3±9.8	79.9±9.8	<0.001
BMI (Kg/m^2)	28.1±5.0	28.4±4.3	27.7±5.7	<0.001
BMI class				<0.001
≤25	3105 (29.0)	1341 (22.2)	1764 (37.7)	
25.1-29.9	4363 (40.7)	2854 (47.3)	1509 (32.3)	
≥30.0	3242 (30.3)	1837 (30.5)	1405 (30.0)	
Familial situation				<0.001
Single	2554 (23.8)	1159 (19.2)	1395 (29.8)	
Couple life	8156 (76.2)	4873 (80.8)	3283 (70.2)	
Educational level				<0.001
≤ high school diploma	4754 (44.4)	2729 (45.2)	2025 (43.3)	
Undergraduate degree	1693 (15.8)	865 (14.3)	828 (17.7)	
Postgraduate degree	4263 (39.8)	2438 (40.4)	1825 (39.0)	
Income of the house/month				<0.001
Less than 1000 €	504 (4.7)	259 (4.3)	245 (5.2)	
1000 – 2099 €	2287 (21.3)	1150 (19.1)	1137 (24.3)	
2100 – 4199 €	5201 (48.6)	2872 (47.6)	2329 (49.8)	
More or equal than 4200 €	2718 (25.4)	1751 (29.0)	967 (20.7)	
Smoking status				<0.001
Non-smoker	4987 (46.6)	2212 (36.7)	2775 (59.3)	
Previous smoker	4523 (42.2)	3122 (51.8)	1401 (30.0)	
Current smoker	1200 (11.2)	698 (11.6)	502 (10.7)	
Alcohol (g/day)	1.4±1.9	1.9±2.2	0.8±1.1	<0.001
Alcohol consumption				<0.001
Never/light	1828 (17.1)	726 (12.0)	1102 (23.6)	
Moderate	7271 (67.9)	4127 (68.4)	3144 (67.2)	
Heavy	1611 (15.0)	1179 (19.6)	432 (9.2)	
Physical activity				<0.001
Sedentary	3082 (28.8)	1847 (30.6)	1235 (26.4)	
Moderate physical activity	4507 (42.1)	2523 (41.8)	1984 (42.4)	
High physical activity	3121 (29.1)	1662 (27.6)	1459 (31.2)	
DASH categories				0.006
Low adherence	1361 (12.7)	764 (12.7)	597 (12.8)	
Medium adherence	8413 (78.6)	4787 (79.3)	3626 (77.5)	
High adherence	936 (8.7)	481 (8.0)	455 (9.7)	
Glycemia	5.9±1.4	6.2±1.5	5.6±1.2	<0.001
Total Chol	5.5±1.1	5.2±1.1	5.8±1.1	<0.001
HDL	1.5±0.4	1.3±0.3	1.6±0.4	<0.001
TG	1.4±0.8	1.5±0.9	1.3±0.7	<0.001
History of CV events	1401 (13.1)	1099 (18.2)	302 (6.5)	<0.001
Diabetes	1661 (15.5)	1168 (19.4)	493 (10.5)	<0.001
Dyslipidemia	6418 (59.9)	3959 (65.6)	2459 (52.6)	<0.001
Chronic kidney disease	178 (1.7)	115 (1.9)	63 (1.4)	<0.001

Data are mean ±SD for quantitative variables or percent for categorical.
Abbreviations: BMI: Body mass index (Kg/m2); BP: Blood pressure; CV: Cardiovascular; DASH, dietary approach to stop hypertension; HDL: High density lipoproteins; SD: standard deviation; TG: Triglycerides;

Figure 1, Proportion of uncontrolled blood pressure among age categories by gender.

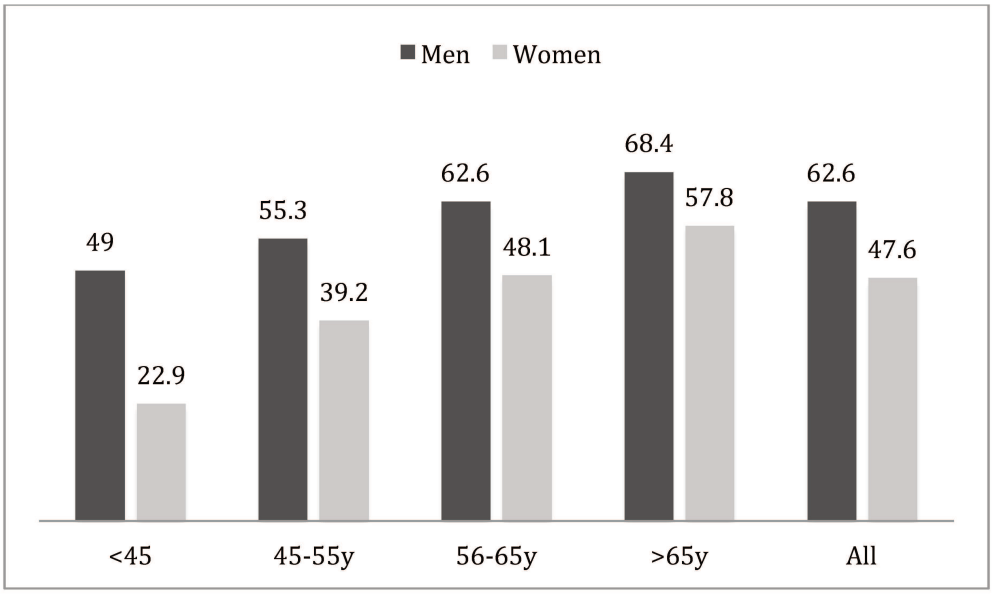

Figure 2, Breakdown of uncontrolled blood pressure based on systolic blood pressure (SBP), diastolic blood pressure (DBP), or both uncontrolled, by gender.

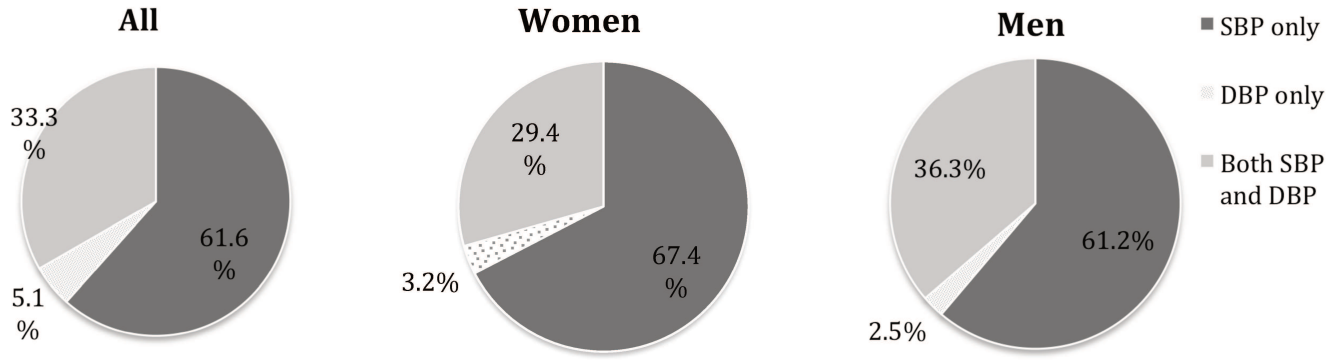

Table 2, Predictors of uncontrolled BP in men

	Uncontrolled BP ORa (95% CI)	***P value***
Age/SD	1.03 (1.02-1.03)	<0.001
Familial situation in couple	1.22 (1.04-1.42)	0.011
Income of the house/month		0.152
Very high (≥ 4200 €)	Ref.	
High (2100 – 4199 €)	1.16 (1.02-1.34)	0.025
Moderate (1000 – 2099 €)	1.12 (0.93-1.36)	0.226
Low (< 1000 €)	1.15 (0.84-1.58)	0.381
Education		0.015
High (post-graduate)	Ref.	
Moderate (undergraduate)	1.25 (1.06-1.49)	0.008
Low (high school or less)	1.17 (1.02-1.33)	0.023
BMI		<0.001
≤25	Ref.	
25.1-29.9	1.20 (1.05-1.38)	0.008
≥30.0	1.49 (1.28-1.75)	<0.001
Physical activity		0.008
High	Ref.	
Moderate	0.83 (0.73-0.93)	0.002
Sedentary	0.85 (0.71-0.98)	0.032
DASH		0.033
High adherence	Ref.	
Medium adherence	1.19 (1.03-1.38)	0.016
Low adherence	1.39 (1.02-1.65)	0.035
Alcohol		0.016
Never/light	Ref.	
Moderate	1.04 (0.88-1.23)	0.650
Heavy	1.26 (1.03-1.54)	0.024
Smoking status		0.094
Non-smoker	Ref.	
Previous smoker	1.09 (0.98-1.24)	0.115
Current smoker	0.90 (0.76-1.09)	0.309
History of CV events	0.56 (0.48-0.64)	<0.001
Diabetes	1.07 (0.99-1.32)	0.065
Dyslipidemia	0.94 (0.83-1.06)	0.346
Chronic kidney disease	0.92 (0.63-1.38)	0.713

Abbreviations: BMI: Body mass index (Kg/m^2); BP: Blood pressure; CV: Cardiovascular; CI: confidence interval; DASH, dietary approach to stop hypertension; ORa: adjusted odds ratio; SD: Standard deviation

Model: adjusted to age, socioeconomic status (marital status, education, income), lifestyle behaviors (BMI, smoking, alcohol consumption, physical activity, DASH) and other risk factors (diabetes, history of CV events, chronic kidney disease, dyslipidemia)

Table 3, Predictors of uncontrolled BP in women

	Uncontrolled BP ORa (95% CI)	***P value***
Age/SD	1.05 (1.04-1.06)	<0.001
Familial situation in couple	1.14 (0.97-1.33)	0.104
Income of the house/month		0.089
Very high (≥ 4200 €)	Ref.	
High (2100 – 4199 €)	0.87 (0.74-1.03)	0.110
Moderate (1000 – 2099 €)	1.03 (0.81-1.27)	0.839
Low (< 1000 €)	1.12 (0.79-1.57)	0.515
Education		0.049
High (post-graduate)	Ref.	
Moderate (undergraduate)	1.01 (0.84-1.20)	0.034
Low (high school or less)	1.18 (1.01-1.37)	0.022
BMI		0.778
≤25	Ref.	
25.1-29.9	1.00 (0.87-1.16)	0.956
≥30.0	0.91 (0.78-1.07)	0.252
Physical activity		0.834
High	Ref.	
Moderate	1.04 (0.89-1.23)	0.587
Sedentary	1.05 (0.91-1.21)	0.513
DASH		0.617
High adherence	Ref.	
Medium adherence	1.15 (0.89-1.49)	0.283
Low adherence	1.19 (0.97-1.45)	0.089
Alcohol		0.376
Never/light	Ref.	
Moderate	1.03 (0.89-1.20)	0.598
Heavy	1.17 (0.93-1.49)	0.173
Smoking status		0.001
Non-smoker	Ref.	
Previous smoker	0.88 (0.77-1.00)	0.058
Current smoker	0.69 (0.56-0.85)	0.001
History of CV events	0.69 (0.54-0.89)	0.003
Diabetes	1.15 (0.94-1.41)	0.149
Dyslipidemia	0.87 (0.77-0.98)	0.034
Chronic kidney disease	1.37 (0.82-2.30)	0.222

Abbreviations: BMI: Body mass index (Kg/m^2); BP: Blood pressure; CV: Cardiovascular; CI: confidence interval; DASH, dietary approach to stop hypertension; ORa: adjusted odds ratio; SD: Standard deviation

Model: adjusted to age, socioeconomic status (marital status, education, income), lifestyle behaviors (BMI, smoking, alcohol consumption, physical activity, DASH) and other risk factors (diabetes, history of CV events, chronic kidney disease, dyslipidemia)

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Discussion and Perspectives

I. Discussion of results

I.a Prevalence, treatment and control of hypertension (article 1 and 4)

In Lebanon, the prevalence, treatment and control (among treated hypertensive) rates were 31.2%, 59.5% and 48.2% respectively. But overall, only 28.7% of patients with hypertension had their blood pressure under control. These figures provide additional evidence of the consistent, elevated prevalence rate of hypertension seen across the world irrespective of the country's income status. Also, the results put to light the associated challenges in treating and controlling the condition and are in accordance with the general rule of halves that is usually referred to in epidemiologic studies **(Hooker *et al.* 1999)**, which is, approximately half the people with high blood pressure are not treated (59.5% treatment rate) and half of those treated are not controlled (51.8% uncontrolled among treated).

Until now, these results are considered the most up-to-date and reliable epidemiologic figures in Lebanon, since the study adopted a population based approach, randomly selecting participants and acting as a nationally representative sample of the Lebanese population. In fact, since then the study has been cited by other researchers when implying epidemiologic data on hypertension in Lebanon **(Azar & Sarkis 2019)**, and are used as reference figures by governmental and public health agencies in Lebanon.

Similarly to Lebanon, the prevalence of hypertension in France was 31.3% and was comparable to another ancillary study conducted on CONSTANCES that reported a prevalence rate of 30.1% **(Neufcourt *et al.* 2019)**. Also, both of these estimated hypertension prevalence rates are consistent with studies on representative French population samples carried out in 2006–2007 (National Health Nutrition Study) **(Godet-Mardirossian *et al.* 2012)** and in 2014–2016 (ESTEBAN) **(Perrine *et al.* 2018)**. Compared to these studies too, the prevalence rate of uncontrolled HTN among treated hypertensive individuals reached 56%, while the ENNS and Esteban studies reported rates of 49.4% and 50.4% respectively. This result suggest that there was no improvement in the control of HTN from 2006 until 2018, despite new recommendations for the management and control

of hypertension and efforts made by the French League Against Hypertension and the French Society of Hypertension **(Mourad *et al.* 2012)**. These numbers are comparable to the approximate 50% control rate among hypertensive treated individuals reported for high-income countries such as in the United States **(Centers for Disease Control and Prevention, 2012)** and Germany **(Neuhauser *et al.* 2015)**.

I.b Association between lifestyle factors and hypertension (articles 1 and 2)

In our analyses, lifestyle factors independently associated with hypertension were: overweight and obesity, physical activity, alcohol consumption and non-adherence to dietary recommendations (DASH-diet). In addition, a combination of unhealthy behaviors significantly and linearly increased the odds of hypertension. We also found that these associations differed slightly between sexes and between the studies on the Lebanese sample and on CONSTANCES.

- **BMI or overweight and obesity**

Both analyses on the association between risk factors and hypertension, either on the Lebanese study (article 1) or on CONSTANCES, consistently show that BMI is the most important lifestyle factor significantly associated with HTN in both sexes. Quantitatively, overweight and obesity (BMI> 25 kg/m2) was found to be the strongest unhealthy behavior associated with around two-fold increase in the odds of hypertension (article 4). This association is further established by finding a gradual somehow linear increase in the odds of HTN across BMI categories. These results are consistent with data from the literature, which places obesity as the main contributor to the increase in the prevalence of hypertension worldwide **(Danaei *et al.* 2011, Must *et al.* 1999)**. In addition, cross-analysis from the French cohort study NutriNet-Santé established that aside from age, BMI is the strongest factor of BP variability among the usual lifestyle behaviors accounting for 7% and 5% of the variance in BP level in women and men, respectively **(Lelong *et al.* 2015)**. Furthermore, recent prospective analyses reported that having a BMI greater than 25 could explain 26% of the incident HTN cases observed in the NutriNet-Santé cohort **(Lelong *et al.* 2017)**. Results of these analyses further ascertain the association between BMI and HTN highlighting the magnitude of the effect of an elevated BMI on the risk of HTN. These

findings further suggest that weight management and maintaining a healthy BMI should be emphasized for the primary prevention of HTN

- **Alcohol consumption**

We found divergent results regarding alcohol consumption and hypertension. In the Lebanese analysis, and in men only, occasional alcohol consumption was found to be protective against developing hypertension (article 1). While in CONSTANCES, heavy alcohol consumption was found to increase the odds of hypertension in both sexes, even after adjustments to other confounding variables. Of note that information about alcohol drinking was limited in the Lebanese questionnaire while it was much more detailed in CONSTANCES, gathering the type and amount of alcoholic beverages consumed; as such, different classification was done and a direct comparison of both results is not possible. Additionally, we believe that in Lebanon, alcohol drinking was underreported because of religious reason, thus influencing the validity of the observed results. Despite these facts, the protective effect of moderate alcohol intake has been previously described in the literature **(Briasoulis *et al.* 2012)**, but in women only contrary to our results. Nevertheless, heavy alcohol intake and risk of HTN was described in numerous studies, in different population and in both sexes **(Arkwright *et al.* 1983, Briasoulis *et al.* 2012)**; but the relationship between light-to-moderate alcohol consumption remains controversial. It appears that the magnitude of the effect of heavy alcohol on hypertension is higher in men than in women and this could be attributed to the differences in the pattern of drinking and beverages choices. Yet, our findings provide additional evidence of the association between heavy alcohol drinking (defined > 21 glass/week (> 210 g/week) for men and > 14 (> 140 g/week) for women) and the risk of hypertension. Of note that the analyses done consider overall alcohol consumption, but some studies favor a difference in effect depending on the type of alcohol consumed, finding in particular, a beneficial effect of wine **(Willett *et al.* 1995)**, because of its polyphenol content. It will be interesting to conduct more in-depth analyses in the future on CONSTANCES study considering not only the amount, but also the type and pattern (with/without meals) of alcohol drinking. Nevertheless, these results support that alcohol consumption should be limited in both men and women **(Williams *et al*. 2018, Whelton *et al.* 2018)**.

- **Physical activity (PA)**

In both analyses (articles 1 and 2) we found an inverse association between PA and hypertension, but in women only. In the Lebanese sample we found a protective association with vigorous PA compared to low-to-moderate. While in the French analyses, physical inactivity compared to high level PA was associated with hypertension. But the magnitude of the effect was small. As described above, the questionnaires used to gather PA level were different in both analyses; therefore a direct comparison is not possible. But this could also mean that regardless of the way PA is measured, increased physical activity (high or vigorous) seemed to be associated with lower risk of hypertension. In general, our results are consistent with data in the literature discussing this association, but in other studies, PA was reported to be strongly and in a dose-related response inversely associated with hypertension **(Huai *et al.* 2013, Pavey *et al.* 2013)**.

Yet, few studies, reported a gender-stratified analysis **(Pavey *et al.* 2013, Azevedo *et al.* 2007)**. The difference in the association between gender could be explained by unreported (missing) occupational or leisure time PA, which is inferred to by the low percentage of individuals classified as low level PA in both analyses. This also questions the performance of the questionnaires used in the estimation of the PA level. In fact, the French questionnaire does not allow the calculation of the corresponding metabolic equivalent, since the type of exercise and exact frequency is not gathered (article 2). This has led to a less reproducible PA score than the literature and different categorization of PA level, therefore influencing the results. Furthermore, the lack of the association in men could be explained by the possibility of an inverse causality bias, which is possible in these types of analyses, whereby individuals with high BP could have increased their level of PA secondary to having hypertension by following lifestyle changes recommendations.

Lastly, the lack of association in men or the only weak association found in women (article 2) could be due to the influence of other socioeconomic or behavioral factors **(Azevedo *et al.* 2007)**; one study based on data from the NutriNet-Santé study explained that BMI is a mediating factor for the effect of physical activity on BP since the level of physical activity and BMI were significantly and inversely correlated **(Lassale *et al.* 2013)**. As such, although globally we found that high PA or being physically active, lowers the risk of hypertension, further prospective studies can help addressing all above mentioned considerations with the aim to better understand the effect of the level of physical activity on hypertension and explain the gender associated differences, if any.

- **Global dietary pattern**

Through this thesis, the effect of a Mediterranean diet adapted to the Lebanese population on hypertension was studied for the first time (article 1). This allowed research data from a nutritional point of view and its influence on hypertension to exist in Lebanon. Detailed nutritional assessment describing the frequency of dietary components of the Lebanese Mediterranean Diet (LMD) between subjects with and without HTN is found in **Appendix 4**. Contrary to what we hypothesized, our results found that those with hypertension had a higher LMDS (better dietary quality). This could be explained by the reverse causality bias, meaning that patients with hypertension are following non-pharmacological recommendations leading to a better adherence to dietary recommendation and not the opposite (better adherence associated with hypertension). In fact, after adjusting to age and other confounders, the association was no longer significant and LMDS was not found to be an independent predictor of hypertension. But importantly, we found that LMDS can influence systolic BP levels (explained below).

On the contrary, French analysis (article 2) found that non-adherence to dietary recommendations, measured by considering a DASH diet-style and calculating a DASH score, to be associated with increased odds of HTN. Association that persisted after adjustment to socioeconomic and other risk factors in both sexes. Also, the magnitude of the effect of non-adherence is pointed out in our results, highlighting a dose-dependent relationship whereby, low adherence (vs. high adherence as reference) is associated with much increased odds of developing hypertension compared to medium adherence (vs. high adherence). Our findings are consistent with data from the literature; even, a recent studies demonstrate that adherence to a DASH-style diet was associated with reduced risk of incident HTN **(Forman *et al.* 2009)**, particularly comparing quartile 4 to quartile 1 **(Lelong *et al.* 2017)**.

We also evaluated the effect of adherence to French dietary recommendations on hypertension, using mPNNS-GS. Results stratified by gender are found in **Appendix 5** and show that similarly to DASH-diet, dietary non-adherence to French recommendations is associated with increased odds of hypertension. These findings should not be too surprising; in fact, the nutritional recommendations of the PNNS have many similarities with the DASH diet, in particular by favoring fruits and vegetables and being low in saturated fats. In addition, the DASH score and the PNNS score were shown to be significantly correlated in a previous study ($r = 0.53$, $p < 0.0001$) **(Lelong *et al.* 2016)**. As

such, these analyses strongly support the association between a global dietary pattern and hypertension, even from different sources of recommendations. The results also quantify the magnitude of the effect of the associations (article 2 and **Appendix 5**); similarly to DASH a dose-dependent response is also found with PNNS with low adherence further increasing the odds of hypertension than medium adherence. Yet, it seems that the magnitude of the effect of DASH is higher than PNNS on the odds of hypertension, but this cannot be concluded from our analyses. This has been seen elsewhere **(Lelong *et al.* 2017)** and suggests that further studies should investigate dietary factors that differ between the two regimes. Nevertheless, the results of this thesis further suggest that adopting a healthy diet through adherence to dietary recommendations can help in the prevention and management of HTN and further support public health directives that aim at improving BP through nutrition.

- **Number of unhealthy behavior**

Cross-sectional analyses conducted on CONSTANCES (article 2) demonstrate that the magnitude of the effect of each of the lifestyle behavior on hypertension is different. The predominant factor found is BMI followed by adherence to a global dietary pattern. But our results show that non-adherence to each of the lifestyle factors (referred to in this case as unhealthy behavior): having a BMI>25, low-to-medium adherence to dietary recommendations, heavy alcohol consumption and sedentary or low level physical activity is associated with a gradual increase in the odds of hypertension. We also studied the combined effect of unhealthy behavior and found that the odds of HTN increased with the number of unhealthy behavior in a nearly linear manner. Individuals with three unhealthy behaviors had more than two-fold increased odds of HTN compared with those without unhealthy behavior. These findings were obtained after adjustment for socioeconomic and cardiovascular risk factors. This indicates that a combination of unhealthy behavior is strongly associated with HTN irrespective of the presence of other risk factors, providing further evidence of the synergistic effect of several lifestyle factors on the prevalence of HTN.

From a population perspective, these results illustrate the importance of behavioral factors and the prevalence of hypertension. This is consistent with data from the literature reporting that a combination of lifestyle factors is associated with further reductions in BP levels **(Blumenthal *et al.* 2010)**. Also, a prospective study of women studied six modifiable

lifestyle variables and found that low-risk combinations of modifiable lifestyle factors were associated with dramatic reductions in the incidence of self-reported HTN during follow-up **(Forman *et al.* 2009)**. Furthermore, the decrease in the risk of incident hypertension associated with adherence to these different measures was found equivalent in subjects with a family history of hypertension suggesting the protective nature of environmental factors even in subjects genetically at greater risk of hypertension. Last but not least, our results are in accordance with recent prospective data evaluating the combined effect of healthy lifestyle behavior on hypertension and complementing our results **(Lelong *et al.* 2019)**. On an individual level, the study reported a linear decrease in the incidence of hypertension; compared with no or one healthy lifestyle factor, the hazard ratios (HR) for hypertension were 0.76 (95% CI, 0.67–0.85) for two factors, 0.47 (95% CI, 0.42–0.53) for three factors and 0.35 (95% CI, 0.30–0.41). On a combined level, compared with adhering to 0, 1, 2 or 3 healthy lifestyles, adhering to all of them was found associated with a reduction of the hypertension risk of half (HR = 0.55 (95% CI, 0.46–0.65)) **(Lelong *et al.* 2019)**. Our finding report the increase risk of hypertension associated with unhealthy behavior, while this study report a decrease in the incidence of hypertension with a healthy lifestyle. These are supportive data that show that active promotion of healthy lifestyle factors at population level is key in the prevention of hypertension.

Lastly, some data argue that the major drawback of lifestyle modification is the poor persistence over time; one study suggested that it appears to be difficult to implement and maintain these lifestyle behaviors in daily life on the long-term **(Goldstein *et al.* 2004)**. Assuming the difficulty to adhere to all these measures in everyday life and to sustain them in the long term, our results imply that there is always a benefit associated with adopting at least one additional measure.

I.c Association between lifestyle factors and uncontrolled hypertension (articles 3 and 4)

The association between lifestyle factors and uncontrolled hypertension is reported in articles 3 and 4; on one side, quantifying the individual and combined effect of lifestyle factors on uncontrolled hypertension (article 3) and on another side determining the extent to which they are independent predictors of uncontrolled hypertension (article 4). Interestingly, these analyses highlighted major differences by gender. Overall and in men only, there was a significant association between uncontrolled hypertension and increased BMI, lower adherence to DASH diet and heavy alcohol consumption. There was unpredictably an inverse association between uncontrolled hypertension and physical activity; in other words, the lower the level of physical activity the lower the odds of uncontrolled hypertension. None of these associations reached significance in women (**Appendix 5**). This gender discrepancy could be attributed to the influence of other confounding variables, such the as the presence of other behavioral factors (salt intake) and differences in lifestyle behaviors between men and women; for example differences in the type and pattern of alcohol drinking. In addition, the number and type of antihypertensive medications used could have affected the results. Also, therapeutic nonadherence (not following recommended medical or health advice, including failure to "persist" with medications and recommended lifestyle modifications) has been reported as a major contributor to poor control of hypertension **(Whelton *et al.* 2018)**. This was seen in one study that identified low medication adherence as a major modifiable risk factor for systolic and diastolic BP control **(Farah *et al.* 20116)**. Furthermore, some data suggest that sex-related characteristics such as the level of sex hormones may influence the results **(Leblanc *et al.* 2015)**. In this context, many women were on contraceptive pills or hormone replacement therapy, which are known to lower the effect of anti-hypertensive treatment and subsequently, could have impacted BP levels and influenced the results. Lastly, the presence of other diseases such as chronic kidney disease and the level of glomerular filtration rate may also act as confounding variables. Although bivariate analysis done and there was no significant difference among these variables in those with or without hypertension, a sex-stratified bivariate analysis and subsequently multivariable models adjusting to these variables could have yielded different results.

- **BMI**

Overweight and obesity, were independently associated with uncontrolled hypertension in men only (article 4), increasing its odds by 1.25-fold and 1.57-fold respectively (article 3). These results are consistent with other studies conducted on individuals being treated for hypertension that reported overweight patients to less likely have their BP under control compared to those with normal BMI **(Ham & Yang 2011)**. As described above BMI appears to be an important factor for the prevalence of hypertension but also for BP control among treated individuals. These findings support that public health efforts directed at improving BP control should target overweight individuals, while emphasize the importance of maintaining a normal BMI.

- **Alcohol consumption**

Heavy alcohol consumption was found to be independently associated with uncontrolled HTN in men only (article 4), with heavy drinkers having 1.34-fold increase in the odds of poor BP control (article 3). These results provide further evidence of the association and support recommendations of limiting or reducing alcohol intake whether for the prevention or control of hypertension.

- **DASH diet**

Low and medium adherence to dietary recommendations were independently associated with uncontrolled hypertension in men only (article 4). Also, low and medium adherence to the DASH diet was found to increase the odds of uncontrolled hypertension by 1.41 and 1.26-fold, respectively (article 3). These results are consistent with results of Menanga et al. reporting adherence to dietary lifestyle changes (OR =1.67; 95% CI: 1.11–2.50; P=0.015) to be independently associated with hypertension control **(Menanga *et al.* 2016)**. Similarly as described for DASH and the odds of hypertension, there seems a linear dose-dependent response between non-adherence to DASH and odds of uncontrolled hypertension, suggesting that lifestyle modifications involving the adoption of a DASH-style diet offer an important approach in the treatment of hypertension.

- **Physical activity**

Surprisingly, the multivariable analysis models found a weak but significant inverse association between physical activity and uncontrolled hypertension (article 4), further

reporting a 0.87-fold decrease in the odds of uncontrolled hypertension (article 3). Some conflicting data exist in the literature, but most studies report a strong relationship between physical activity and good BP control. The reasons behind our controversial results are the same as explained in he above part "association between unhealthy behavior and hypertension", particularly because we used a less reproducible PA score from the literature and that we did not calculate the corresponding metabolic equivalent (MET) for the type of reported physical activity. Further studies are necessary to assess this aspect.

- **Smoking**

Unconventionally, our results found current smoking to be associated independently with decreased prevalence of uncontrolled hypertension (article 4). Epidemiological studies describe discrepancy with regards to effect of smoking on uncontrolled BP; some studies reported smoking to negatively influence BP control **(Rosendo *et al.* 2017, Choudhary *et al.* 2016)**, while others found no association **(Asgedom *et al.* 2016, Farah *et al.* 2016)** and showed that office BP is not lowered by smoking cessation **(Primatesta *et al.* 2001)**. Further research can help yield more conclusive results. Nevertheless, smoking is an unhealthy behavior and a major risk of CVD and cancer; smoking cessation recommendations should be provided to all hypertensive individuals for the prevention of CVD including stroke, myocardial infarction and peripheral artery disease.

- **Number of unhealthy behavior**

Our results show a nearly linear association between the number of unhealthy behaviors and uncontrolled hypertension, with odds increased continuously with 1, 2, 3 or more unhealthy behaviors, but reached statistical significance with 3 or more factors. Details are found in discussion part of article 3, but briefly, these results show here again that lifestyle changes should employ a multidisciplinary approach that includes weight loss, healthy diet and limitation of alcohol consumption; this approach can offer considerable benefit in the management of hypertension.

I.d Influence of socio-economic factors on hypertension and BP control (article 1 and 4)

Some observational data report disparities in the prevalence of hypertension **(De Gaudemaris *et al.* 2002, Panagiotakos *et al.* 2008)** and, more broadly, cardiovascular risk **(Elovainio *et al.* 2011, Panagiotakos *et al.* 2008, Damiani *et al.* 2010)** according to the socio-economic status of individuals. These findings were seen in various Western populations, both American **(Mensah *et al.* 2005)** and European populations **(Elovainio *et al.* 2011, Panagiotakos *et al.* 2008)**.

Some studies suggest that nutritional, dietary or behavioral factors are mediating factors that explain the relationship between poorer socio-economic status and increased level of BP. In other terms, a lower socioeconomic status is associated with a poorer lifestyle risk profile such as diet and exercise and, in turn, with higher SBP **(Chaix *et al.* 2010)**. Thus, a review of the literature places BMI as the primary mediator of this relationship, especially in women **(Colhoun *et al.* 1998)**. Results from another study in Spain suggest that dietary quality may explain part of the relationship between cardiovascular risk factors and lower socioeconomic status **(Panagiotakos *et al.* 2008)**.

We studied the influence of socioeconomic factors on hypertension (article 1) and on uncontrolled hypertension (article 4). From a descriptive point, both cross-sectional analyses strikingly found same SES indices associated with either hypertension or uncontrolled hypertension. In fact both analyses demonstrated that a lower level of education to be significantly and inversely associated with hypertension in women (article 1) and with uncontrolled hypertension in both sexes (article 4). Additionally, both analyses found that marital status (or living in couple in CONSTANCES) to be associated with hypertension and uncontrolled hypertension in men only.

In addition, lower socioeconomic status is associated with unhealthy lifestyle factors. In fact, analyses show that lower education and lower household monthly income to be associated with a higher number of unhealthy behavior (articles 2 and 3). This supports the above-mentioned statement that a lower SES is associated with poorer lifestyle risk factors, which could increase the risk of hypertension. In fact, SES factors were not found as a modulatory factor of the relationship between lifestyle factors and hypertension (article 2) when

conducting analyses using models adjusted to SES factors. This suggests that a DASH diet, reduction in alcohol, normal BMI and physical activity to have beneficial protective effect regardless of the socio-economic level of the participants (Article 2).

On the other hand, both cross-sectional analyses show that hypertension is inversely associated with education level regardless of BMI, alcohol, dietary pattern and level of physical activity (multivariable models in articles 1 and 4). Therefore, we cannot completely disregard the fact that socioeconomic factors could be independently associated with hypertension. These associations have been seen in other studies discussion the independent effect of education level on hypertension **(Lelong *et al.* 2016)** and on uncontrolled hypertension **(Polonia *et al.* 2014)**. The level of education is thought to be a crucial socioeconomic measure as it can be reliably recalled and unaffected by later adult health, and was suggested to be the most important socioeconomic factor with an impact on HTN **(Rosendo *et al.* 2017)**. Although the reasons for the gender-related difference remain unclear, lower level of education can justify unhealthy lifestyle habits that could influence behaviors (diet, smoking, exercise and alcohol) **(Vargas *et al.* 2000)**. They could also have poor access to healthcare. As such, maybe more health-education efforts on BP control among treated individuals of lower education level ought to be directed.

As for marital status, conflicting results exist in the literature with regards to this association. Yet, our results are consistent with those reported in other studies **(Farah *et al.* 2016, Choudhary *et al.* 2016)**. Perhaps, psychological stress, which could be caused by occupational or familial stressors, could influence the observed results. The reasons behind this gender discrepant result should be further investigated.

I.e Relationship between lifestyle factors and blood pressure level (articles 1 and 4)

Evaluation of the relationship between lifestyle behaviors of interest and SBP in an age-adjusted model was conducted on the Lebanese sample (article 1) and on treated hypertensive individuals from the CONSTANCES study (article 4 and **Appendix 7**). From a descriptive standpoint, healthy lifestyle factors were overall associated with lower SBP, with few exceptions.

- **BMI**

BMI appears as the most important factor influencing systolic blood pressure level. Both Lebanese and French analyses found a significant increase in SBP across BMI categories and in both sexes. These results reinforce again and again that BMI appears as the most important factor associated with hypertension and influences BP levels. In the general population (article 1), a difference of around 6mmHg was found between BMI<25 and >30, while on hypertensive treated individuals (article 4), the magnitude of BP variability was of a lesser extent (around 2 mmHg). These results underline the importance of weight loss in overweight and obese individuals and the achievement of a normal BMI can help in preventing, managing and improving BP control.

- **Dietary pattern scores**

The effect of a global dietary pattern was evaluated through 3 scores: DASH, mPNNS and LMDS. French analyses (**appendix 7**) found that SBP was significantly lower with better DASH adherence levels (around 3 to 4 mmHg reductions) in men and women. While for the mPNNS, SBP reductions were found across adherence levels but the association reached significance in men only (around 5 mmHg reductions). On the contrary, Lebanese analysis (article 1) found significant decrease in SBP level with better adherence to LMDS in women only (around 2mmHg). Notably these results show that the degree of SBP reductions is different between the three scores, but they indicate that a quality dietary pattern is beneficial on the BP in a variety of populations; either on the general population (article 1) and on hypertensive treated subjects (article 4); but that the magnitude of the effect and the extent of the association is different between study populations. Moreover, the degree of SBP reduction seems lower compared to the hypotensive effect of the DASH regimen reported by the intervention trials **(Saneei *et al.* 2014, Harrington *et al.* 2013)**, but this is

expected given the retrospective nature of our analyses and differences in statistical adjustments. Interestingly, our results are consistent with data from NutriNet-Santé study, conducted on untreated individuals, who reported that the amount of the effect associated with the 3 scores (DASH, mPNNS and MD) on SBP level to be comparable even when evaluated through standardized scores **(Lelong *et al.* 2016).** Although our results are not conclusive as several adjustments for additional confounders should be made, but they support that dietary adherence influences BP levels. Prospective data could help better determining the extent to which dietary adherence influence BP levels in different study populations, differences between scores and the reasons behind gender disparities.

- **Alcohol consumption**

Analyses of the thesis evaluated the influence of alcohol consumption on SBP, using 2 indicators of alcohol use: Alcohol consumption classes (g/week) and the AUDIT (alcohol used disorder identification test, explained in details in the methodology part of this thesis). Results of these analyses are found in **Appendix 7**, whereby we found a significant increase in the mean SBP across ascending classes of both variables, in both sexes. We found a difference of 3mmHg across alcohol consumption classes, which is comparable to the level of BP reductions reported by alcohol reduction from randomized trials. For example, a meta-analysis of 36 studies involving 2865 participants revealed that reduction in alcohol intake from 06 drinks/week to 03 drinks per week resulted in 5.5 mmHg reduction in SBP and 3.97 mmHg in DBP **(Roerecke *et al.* 2014).** On the other hand, we found a BP difference of 15mmHg across AUDIT categories from no abuse to dependence, which seems excessive. In general, there are some variations in the level of SBP reductions associated with reduction of alcohol intake; these differences are based on baseline drinking habits, amount of alcohol reduction, duration of the trials and patient population. Although as mentioned before the results are not conclusive, they definitely encourage more research to be conducted on alcohol and BP levels, evaluating not only quantity and frequency of alcohol use but also drinking behavior, pattern (including binge drinking), and differences in types of beverages, which could have influence the degree seen here.

- **Psychological stress**

Influence of psychological distress on BP level was studied in the Lebanese and French studies, using the BDS-22 score (Beirut distress scale; article 1) and the CES-D score (Center of Epidemiologic Studies Depression scale; **appendix 7**). Both scores are detailed in the methodology part of the thesis and the descriptive results of the BDS-22 are found in **Appendix 4**. In brief, there was no relationship between BDS-22 nor CES-D and SBP in both men and women. This questions the effect of psychological stress on BP levels on different study populations, and whether stress management could influence BP levels in terms of prevention and control of hypertension. Nevertheless, these results are non-conclusive and could not rule out the influence of stress on BP levels. In fact, another analysis on CONSTANCES, found that there's an increase in coronary heart disease risk in those with depressive symptoms measured by the CES-D (compared to those without), which was more pronounced as occupational status decreased, implying that the association between CHD and psychological stress is mediated and different based on the SES of individuals **(Wiernik *et al.* 2018)**. Accordingly, in order to provide additional evidence of the effect of psychological stress on BP, analyses should be conducted stratified over the different SES indicators. Keeping in mind also the evaluation of psychological stress from its different sources including psychological, social and occupational perspective. As such, future research should consider tools able to determine stress with its different forms.

- **Physical activity**

Effect of physical activity on BP level was evaluated in CONSTANCES, after finding a barely significant association with hypertension and an unexpectedly inverse association with uncontrolled hypertension. Here again, there was an inverse relationship between mean SBP and physical activity levels (**Appendix 7**), with SBP levels increasing with increased PA level. Our results contradict data from the literature reporting the beneficial effect of physical activity on BP level, this further questions the ability of the questionnaire determine appropriately the physical activity level, leading to a less reproducible score than the literature.

II. Methodological considerations

II.a Quality of the data collected

Like most epidemiological studies, the Lebanese study and CONSTANCES study are based on self-reported data and are therefore subject to reporting bias. However, as we saw in the chapter materials and methods, data was collected through multiple sources, some variables were "pre-calculated" and many measurements were standardized, that is performed following standard operational procedures. In addition, many validation studies were conducted either on the Lebanese study or by CONSTANCES team evaluating the quality of data.

- For both studies, the quality of the anthropometric data is excellent. SOPs existed for each measurement, and a healthcare practitioner collected data thus, reducing the risk of desirability bias.
- On the other hand, lifestyle behaviors were self-reported, thus introducing misclassification and desirability bias when relying on the participants to report risk factors; as a consequence this may lead to underreporting of unhealthy behavior, influencing the lack of significant associations with certain variables. However the questionnaires used were exhaustive, common and reliable.
- For capturing nutritional behavior, both studies used food-frequency questionnaires (FFQ) to evaluate a global dietary pattern, using trustworthy tools and scores to capture dietary adherence
    - In the Lebanese study we used a FFQ adapted to the Lebanese population and used the LMDS, which is a score created and computed from a FFQ. In addition LMDS is reliable, as it has been previously validated **(Issa *et al.* 2014)**. However, some disadvantages to the use of this instrument is that it makes components equally weighed and similarly scored from 0 to 4 giving all foods same effect on HTN and BP and which may not be true. In addition it doesn't considers intake of salt and neither alcohol nor it takes into account the total energy intake. Furthermore, it hasn't been directly compared to DASH or mPNNS to evaluate their correlation. Nevertheless, previous studies show that the LMDS is in adherence to a Middle Eastern version of the MD, being correlated with European MD scores and standing

closest to the Italian **(Naja *et al.* 2015)**. Also this type of dietary indexes is simple and has been extensively used in epidemiological studies.

- In CONSTANCES study, we computed DASH and mPNNS scores form the FFQ, which is not the optimal approach as these scores are computed from a quantitative food-based approach. In fact, responses considering the type of foods and frequency of the consumption were converted to approximate amount (in grams/day) of dietary components included in the DASH and mPNNS. Another drawback from this approach is the estimation of salt intake based on the type of food consumed, questioning the accuracy of such a technique. Nevertheless, this method of calculating a DASH score has been widely used in epidemiologic studies.
- The study of individual consumption of dietary components (proteins, fiber, fats…) and salt intake on hypertension and BP levels was not possible through the FFQ. However, it wasn't also one of the objectives of this thesis.

- Alcohol intake was assessed in the CONSTANCES study through questionnaires gathering, amount, frequency, type and pattern of alcohol drinking. This gave opportunity to evaluate the influence of alcohol on hypertension and BP levels considering several definitions of alcohol use. On the opposite, we considered alcohol intake inaccurate in the Lebanese study and under-reported as many individuals might have misreported intake because of their religious beliefs. Therefore acting as a limitation for the Lebanese cross-sectional analyses.
- Physical activity was determined in the Lebanese study following the IPAQ questionnaire and considering the MET of activities; a common method used in the literature for assessing PA. While the CONSTANCES study used a less reproducible score, which does not allow close comparison of results with other studies. This was a limitation of the studies conducted throughout this thesis, especially since unexpected results have been reported in the different analyses (articles 2, 3 and 4).
- The quality of heath data differs between both studies. The Lebanese study relies on self-reported health data and medical treatment, thus data being subject to recall bias. While the CONSTANCES study gathers socio-demographic as well as health and medical data through different methods and sources: self-reported using questionnaires and non-dependent on individuals while relying on national and health databases. For the analyses conducted in this thesis we relied on self-

reported information and use of medications from national reimbursement database. The quality of the health data should be studies by comparing the reported data with the SNIIRAM data on at least a subsample.

- Regarding hypertension data involving both studies, current practice guidelines recommend that the diagnosis of hypertension be based on at least two BP measurements per visit (which was done) and on at least two visits; which is not feasible in large population studies. Although this might influence the prevalence of hypertension this approach is supported and commonly adopted in epidemiological studies. More importantly is that the definition of prevalent hypertension and uncontrolled hypertension is detailed and illustrated in algorithms in the "materials and methods part of this thesis", considering several possible scenarios, thus suggesting the estimation of adequate prevalence and control rates especially when considering use of anti-hypertensive medication obtained from the national reimbursement database.
- Moreover, the Lebanese survey did not address questions related to awareness of hypertension and therefore results did not follow the traditional epidemiologic description of prevalence, awareness, treatment and control of hypertension. The CONSTANCES study did so, but was not part of the analyses of this thesis
- Lastly, psychological distress was assessed using reliable instruments. The BDS-22 and the CES-D were used, both instruments being validated in the Lebanese and French population, respectively. But a limitation of using these instruments is their inability to gather occupational and social stressors, thus possibly leading to the lack of association between psychological stress and hypertension.

II.b Representation of the population and generalization of results

The main strength of our analyses is the use of large samples, which ensure sufficient power to detect associations, as well as adopting a population-based approach using a representative randomly selected sample of participants. In fact the Lebanese sample is a nationally representative sample, while CONSTANCES included a sample representative of the CNAMTS. However several limitations must be addressed

- CONSTANCES included individuals covered by the CNAMTS, i.e. salaried workers whether they are professionally active, unemployed or retired and their family accounting for more than 85% of the French population. But, agricultural workers and self-employed workers were excluded and therefore the population may not be representative of the general population.
    - In order to tackle this limitation, a collaboration was established with the COSET project managed by the Occupational Health Department of the National Institute for Health Surveillance, which is currently setting up two complementary cohorts, one of agricultural workers and one of self-employed persons which were designed in a way that data sharing with CONSTANCES will be possible **(Goldberg *et al.* 2016)**.
- Furthermore, as for many epidemiological investigations, there might be a selection effect, on one side caused by the low participation rate (7.3% for CONSTANCES) and on another side because of the voluntary participation nature in these studies. This results in typically healthier, higher educated and more health conscious volunteers who participate in such investigations **(Rothman *et al.* 2013)** making it difficult to extrapolate findings to the French population.
    - The low participation rate was comparable in magnitude to other similar cohorts, like UK Biobank in which the participation rate is 5.47%
    - In addition, to take into account selection effects (non-participation and attrition) due the voluntary participation the following was done:
        - A "control cohort" was drawn from a random sample of 400 000 non-participants, that is, persons who were invited but did not participate, for whom social and occupational, health and healthcare usage data were prospectively collected from the same administrative databases as for the volunteer participants **(Goldberg *et al.* 2016)**
        - Using reweighting techniques relying on the "control cohort"

II.c Reverse causality in cross-sectional studies

All of the analyses conducted in this thesis are based on cross-sectional analyses evaluating the association between hypertension and lifestyle factors, so it may be difficult to ascertain the temporal order of lifestyle changes and hypertension and thus it may not be possible to establish a causal relationship. In fact participants may have modified their lifestyle habits in response to raised BP, introducing a reverse-causality bias, which is inherent in this type of analysis. For example, in article 1 those with hypertension had higher LMDS score indicating better adherence to dietary recommendation, these participants could be theoretically following non-pharmacological measure as recommended. In the same line of thinking, participants with uncontrolled hypertension in article 4 had higher level of physical activity.

III. Conclusion and Future Research Questions

Our results provided needed epidemiologic data on hypertension in Lebanon. Certainly, they showed that hypertension and poor BP control are highly prevalent and for the first time the association between hypertension and dietary factors using a score adapted to the Lebanese diet, was discussed. On a broader level, our findings show that non-adherence to widely recommended lifestyle modifications for the management of hypertension could increase the risk of hypertension and has a major influence on BP control. Increased BMI, heavy alcohol consumption and non-adherence to dietary recommendations were seen to be independently associated with hypertension and poor BP control, and they influence systolic BP levels. In terms of the magnitude of the effect of the association, BMI and adherence to DASH diet and to a lesser extent to PNNS recommendations seem to have the biggest impact on increasing the odds of hypertension and uncontrolled BP. Moreover, the quantitative estimate of the combined association between unhealthy behavior and hypertension highlighted the effect of an overall poor lifestyle on the risk of hypertension. Furthermore our findings suggest that the extent to which these factors are associated with hypertension is different by gender. From a population-based perspective, these findings promote that a global healthy lifestyle through improvement of modifiable behaviors could have major benefits in the prevention of hypertension. Given the increasing prevalence of hypertension and associated health implications, the promotion and implementation of these non-pharmacological measures is important form a public health standpoint.

In Lebanon, further studies on hypertension and blood pressure control are needed. Also, In the future, data from the CONSTANCES cohort study, may allow further investigations directly related to the work of this thesis:

- First of all, it will be necessary to evaluate the association between lifestyle factors and incident hypertension and to evaluate the extent to which these factors influence the development of hypertension.
- Also it would be important to study the impact of these factors on cardiovascular morbidity and mortality with the purpose of improving BP level in the population
- Additionally, future research should address the gender-based differences that were preliminary observed from this thesis and potentially understand the reasons behind these discrepancies.
- Some factors warrant further evaluation from a different perspective, such as:

- Alcohol consumption including the type of beverages and pattern of drinking (drinking outside meals, binge drinking)
- Physical activity including physical activity at work and outside of work, with closer attention to the score used and the possibility of calculating MET of activities
- Correlation of the different dietary scores and the evaluation of not only global dietary pattern but also dietary components, from a quantitative point of view; this has been extensively studied in the French NutriNet-Santé study
- Smoking status, including the emerging social use of the waterpipe (Chicha) and e-cigarettes and their effect on ambulatory blood pressure.
- Psycho-social factors, especially stress and depression. Although we briefly studied the influence of stress on BP levels, as discussed before future research should study the influence of psychological stress through stratified-analyses, conducted over the different SES indicators. Also, the different sources of stress should be considered (psychological, social and occupational). This contemporary subject is important, as stress management is a recommended approach in the management of hypertension in the latest Canadian guidelines **(Nerenberg et al. 2018)**.

- Data from the literature suggest that other environmental factors influence blood pressure. As such future research can evaluate their effect.
    - Exposure to air pollution and air pollutants could have a negative impact on the cardiovascular system and especially on BP. In fact, epidemiological data reported an increase in the systolic BP of 1 mmHg for each increase of 10µg/m3 of fine particles in the air. This may seem unimportant but should be considered especially when exposed up to 60 µg / m3 of fine particles in the air during periods of winter heating or pollution peaks in certain urban areas **(Chan et al. 2015)**. Both questionnaire, CONSTANCES and the Lebanese capture participants' exposure to outdoor and indoor air pollution, even the Lebanese study measure the participants exhaled carbon monoxide, all of which could be used in assessing the effect of air pollution o hypertension. Furthermore, geolocation of participants could be used to study this relationship.

- Sleeping habits is another subject discussed in the literature. Both sleep deprivation and insomnia have been linked to increases in incidence and prevalence of hypertension **(Cappuccio et al. 2007).** This is explained that in insomnia, the hypothalmic-pituitary-adrenal axis and the sympathetic nervous system are activated, which may predispose to hypertension development. This association could be studied from CONSCTANCES study as the questionnaire gathers information about sleeping habits (Bonnet 2009).

- Considering all above factors, CONSTANCES offers the possibility to undertake the same analyses and to take into consideration most of the potential confounding factors.
- Moreover, evaluation of medical treatment including type and number of anti-hypertensive, regimen adjustments and adherence to treatment, in cross-sectional and prospective analyses will allow better understanding of the management of hypertension in France, with an insight into its influence on the control of hypertension.
- Also, because of the annual follow up of participants through questionnaires, and thus the obtainment of prospective data on lifestyle behavior, we could evaluate the impact of the implementation of public health recommendations on BP. On one hand, we can evaluate adherence to the various recommendation over time and particularly to various new recommendations evolving in time. On the other hand the impact in terms of occurrence/incidence of hypertension.
- In addition, SES factors as well as professional context and hypertension could be further elaborated in CONSTANCES, because of the extensive availability of socio-demographic data and contextual pre-calculated variables by Sicore.
- Lastly, the presence of other large ongoing epidemiologic studies, such as the Esteban study and NutriNet-Santé study provide exhaustive data and extensive opportunities for exploration of factors acting as determinants of hypertension in different study populations. These studies also from their prospective nature allow determining preventive strategies aiming at the prevention, delay or management of hypertension. It will be interesting to compare the results of these studies to CONSTANCES'

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Appendices

Appendix 1

Food consumption benchmarks of the revised National Health Nutrition Program (2017-2021); the PNNS 4.

LES REPERES ALIMENTAIRES POUR LES ADULTES (*HCSP, 2017*)		
Fruits et légumes		Au moins 5 par jour
Fruits à coque sans sel ajouté (*amandes, noix, noisettes, pistaches*)		Une petite poignée par jour
Légumineuses (*légumes secs : lentilles, pois chiche, haricots…*)		Au moins 2 fois par semaine
Produits céréaliers complets peu raffinés (*pain, pâtes, riz…*)		A consommer tous les jours, en privilégiant les produits complets ou peu raffinés par rapport aux produits raffinés.
Produits laitiers (*lait, yaourts, fromage et produits laitiers dans les plats cuisinés*)		2 produits laitiers par jour
Viande et volaille		Limiter la consommation de viande rouge et privilégier la consommation de volaille.
Poisson et fruits de mer		2 fois par semaine (dont 1 poisson gras)
Charcuterie		Limiter la consommation
Matières grasses ajoutées		Eviter les consommations excessives. Privilégier les huiles de colza et de noix (riche en ALA) et l'huile d'olive sans augmenter la consommation habituelle de matières grasses ajoutées
Produits sucrés		Limiter la consommation de produits sucrés
Boissons		La seule boisson recommandée est l'eau (à volonté)
Sel		Réduire la consommation de sel

Appendix 2

List of anti-hypertensive medication listed by pharmacological class and generic name

	Diuretics		**Beta Blockers (BB)**		**Calcium Channels Blockers (CCB)**
Thiazide and thiazide like	**Hydrochlorothiazide** **Chlorthalidone** **Indapamide** Bendroflumethiazide Hydroflumethiazide Chlorothiazide Polythiazide Trichloromethiazide Cyclopenthiazide Methclothiazide Cyclothiazide Mebutizide Metazolone Clopamide	**Non-selective**	**Propranolol** **Nadolol** **Sotalol** Alprenolol Oxprenolol Pindolol Timolol Mepindolol Carteolol Tertatolol Bopindolol Bupranolol Penbutolol Cloranolol Carazolol	**Dihydropyridine CCBs**	Amlodipine Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Lacidipine Nilvadipine Manidipine Barnidipine Lercanidipine Cilnidipine Benidipine Clevidipine
Loop	**Furosemide** **Bumetanide** Torademide Piretanide Etacrynic acid Tienilic acid	**Selective**	**Atenolol** **Bisoprolol** **Metoprolol** **Esmolol** **Nebivolol** **Acebutolol** **Betaxolol** Practolol Bevantolol Celiprolol Epanolol Talinolol Landiolol	**Non-DHP CCBs**	**Diltiazem** **Verapamil**
Potassium sparing-aldosterone antagonists	**Spironolactone** **Epleronone** Canrenone				
Potassium sparing-others	**Amiloride** **Triamterene**				
		Alpha and beta blocking	**Carvedilol** Labetolol		

In Bold: Most commonly used agents
*Not reimbursed (covered) by insurance

BB and CCB	**Non-selective BB and Thiazides**	**Selective BB and Thiazides**
Metoprolol and felodipine Atenolol and nifedipine Bisoprolol and amlodipine Nebivolol and amlodipine Metoprolol and amlodipine	Oxprenolol and thiazides Propranolol and thiazides Timolol and thiazides Sotalol and thiazides Nadolol and thiazides Metipranolol and thiazides, combinations	Metoprolol and thiazides Atenolol and thiazides Acebutolol and thiazides Bevantolol and thiazides Bisoprolol and thiazides Nebivolol and thiazides Metoprolol and thiazides, combinations
Other combinations		**CCB and diuretics**
Metoprolol and ivabradine Carvedilol and ivabradine		Nifedipine and diuretics Amlodipine and diuretics

ACE inhibitors	**ACE inhibitors and CCB**	**ACE inhibitors and diuretics**
Captopril **Enalapril** **Lisinopril** **Perindopril** **Ramipril** **Quinapril** **Benazepril** Cilazapril Fosinopril Trandolapril Spirapril Delapril Moexipril Temocapril Zofenopril Imidapril	Enalapril and Lercanidipine Lisinorpil and amlodipine Perindopril and amlodipine Ramipril and felodipine Enalapril and nitrendipine Ramipril and amlodipine Trandolapril and verapamil Delapril and manidipine	Captopril and diuretics Enalapril and diuretics Lisinopril and diuretics Perindopril and diuretics Ramipril and diuretics Quinapril and diuretics Benazepril and diuretics Cilazapril and diuretics Fosinopril and diuretics Delapril and diuretics Moexipril and diuretics Zofenopril and diuretics
		Other combinations
		Perindopril, amlodipine and indapamide Perindopril and bisoprolol Ramipril, amlodipine and HCTZ Benazepril and pimobendan

In Bold: Most commonly used agents
*Not reimbursed (covered) by insurance

ARB	ARB and CCB	ARB and diuretic
Losartan **Valsartan** **Irbesartan** **Candesartan** **Telmisartan** Eprosartan Tasosartan Olmesartan* Azilsartan Fimasartan	Valsartan and amlodipine Olmesartan and amlodipine Telmisartan and amlodipine Irbesartan and amlodipine Losartan and amlodipine Candesartan and amlodipine Valsartan and lercanidipine	Losartan and diuretics Eprosartan and diuretics Valsartan and diuretics Irbesartan and diuretics Candesartan and diuretics Telmisartan and diuretics Olmesartan and diuretics Azilsartan and diuretics Fimasartan and diuretics
		Other combinations
		Valsartan, amlodipine and HCTZ Valsartan and aliskiren Olmesartan, amlodipine and HCTZ Valsartan and sacubitril

In Bold: Most commonly used agents
*Not reimbursed (covered) by insurance

Alpha-2 agonists	Alpha-1 antagonists	Renin Inhibitors	Others
Methldopa **Clonidine**	Prazocin Indoramin Trimazocin Doxazocin Urapidil	Remikiren Aliskiren* Aliskiren and HCTZ Aliskiren and amlodipine Aliskiren and HCTZ and amlodipine	

In Bold: Most commonly used agents
*Not reimbursed (covered) by insurance

Appendix 3

3.1 Construction of the modified Programme National Nutrition Santé - Guideline Score (mPNNS-GS)

	Recommendation*	Scoring criteria**	Score
1. Fruits and vegetables	At least 5/d	[0-3.5] [3.5-5] [5-7.5] ≥7.5	0 0.5 1 2
2. Bread, cereals, potatoes and legumes	At each meal according to appetite	[0-1] [1-3] [3-6] ≥6	0 0.5 1 0.5
3. Whole grain food	Choose whole grains and whole grains breads more often	[0-1/3] [1/3 - 2/3] ≥2/3	0 0.5 1
4. Milk and dairy products	3/d (≥ 55-years old: 3 to 4/d)	[0-1] [1-2.5] [2.5-3.5] *(≥ 55-years old: [2.5-4.5])* >3.5 *(≥ 55-years old: >4.5)*	0 0.5 1 0
5. Meat, poultry seafood and eggs	1 to 2/d	0 [0-1] [1-2] >2	0 0.5 1 0.5
6. Seafood	At least 2/week	<2/week ≥2/week	0 1
7. Added fats	Limit consumption	Lipids from added fat >16% EI*** /d Lipids from added fat ≤16% EI*** /d	0 1
8. Vegetable added fats	Favor fats of vegetable origin	No use of vegetable oil or ratio vegetable oil/total added fat ≤0.5 No use of added fats or ratio vegetable oil/total added fat >0.5	0 1
9. Sweetened foods	Limit consumption	Added sugar from sweetened foods ≥17.5% EI***/d Added sugar from sweetened foods 17.5-12.5% EI***/d Added sugar from sweetened foods <12.5 % EI***/d	-0.5 0 1
10. Non-alcoholic beverages (water and sodas)	Drink water as desired Limit sweetened beverages: no more than 1 glass/d	< 1L water and > 250 ml soda/d ≥ 1L water and > 250 ml soda/d < 1L water and ≤ 250 ml soda/d ≤ 1L water and ≤ 250 ml soda/d	0 0.5 0.75 1
11. Alcoholic beverages	Women advised to drink ≤2 glasses of wine/d and men ≤3 glasses/d	Ethanol > 20 g/d for women and > 30g/d for men Ethanol ≤ 20 g/d for women and ≤ 30g/d for men Abstainers and irregular consumers (< once a week)	0 0.8 1

12. Salt	Limit consumption	>12g/d	-0.5
		[10-12] g/d	0
		[8-10] g/d	0.5
		[6-8] g/d	1
		≤6 g/d	1.5
13. Physical activity	At least the equivalent of 30 min of brisk walking per day	[0 – 30 min /d]	0
		[30 – 60 min /d]	1
		≥ 60 min /d	1.5

*Recommendations of the Programme National Nutrition Santé (PNNS)
** serving per day unless otherwise indicated
***EI: energy intake without alcohol

3.2 Development of the DASH adherence score according to Fung et al.2008

Component	Foods	Scoring Criteria	Q1, Servings/d	Q5, Servings/d
Fruits	All fruits and fruit juices	Q1 = 1 point	0.7	4.1
Vegetables	All vegetables except potatoes and legumes	Q2 = 2 points	1.1	4.6
Nuts and legumes	Nuts and peanut butter, dried beans, peas, tofu	Q3 = 3 points	0.3	1.5
Whole grains	Brown rice, dark breads, cooked cereal, whole grain cereal, other grains, popcorn, wheat germ, bran	Q4 = 4 points Q5 = 5 points	0.1	2.4
Low-fat dairy	Skim milk, yogurt, cottage cheese		0.1	2.3
Sodium[b]	Sum of sodium content of all foods in FFQ	Reverse scoring: Q1 = 5 points	1041 mg	2676 mg
Red and processed meats[b]	Beef, pork, lamb, deli meats, organ meats, hot dogs, bacon	Q2 = 4 points Q3 = 3 points	0.4	1.8
Sweetened beverages[b]	Carbonated and noncarbonated sweetened beverages	Q4 = 4 points Q5 = 1 point	0	1.2

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; FFQ, food frequency questionnaire; Q, quintile.
[a] Mean of 5 FFQs.
[b] Higher quintiles represent higher intake; however, in constructing the DASH score, high intake and high quintiles received lower scores.

Appendix 4

Additional and supplementary results from article 1

Table 1. Nutritional assessment between patients with and without HTN

Nutrition	Never	≤ *2x per week*	*3-6x per week*	*Once a day*	*At every meal*	*P*
Raw Vegetables						
HTN	9 (1.8)	150 (29.9)	160 (31.9)	169 (33.7)	14 (2.8)	
Non-HTN	14 (1.3)	307 (28.2)	366 (33.6)	352 (32.3)	51 (4.7)	
Fast food						*
HTN	186 (37.3)	251 (50.4)	45 (9.0)	15 (3.0)	1 (0.2)	
Non-HTN	206 (19.0)	566 (52.3)	218 (20.1)	93 (8.6)	0 (0)	
Fried foods						*
HTN	76 (15.1)	253 (50.4)	110 (21.9)	53 (10.6)	10 (2.0)	
Non-HTN	86 (7.9)	460 (42.1)	318 (29.1)	210 (19.2)	18 (1.6)	
Olive oil						***
HTN	12 (2.4)	57 (11.4)	66 (13.2)	276 (55.1)	90 (18.0)	
Non-HTN	19 (1.8)	127 (11.8)	213 (19.7)	529 (49.0)	192 (17.8)	
Food grains						
HTN	13 (2.6)	276 (55.3)	156 (31.3)	45 (9.0)	9 (1.8)	
Non-HTN	28 (2.6)	595 (55.1)	353 (32.7)	91 (8.4)	13 (1.2)	
Fish or sea food						***
HTN	41 (8.2)	376 (75.7)	59 (11.9)	15 (3.0)	6 (1.2)	
Non-HTN	71 (6.6)	764 (71.3)	193 (18.0)	35 (3.3)	9 (0.8)	
All meat						*
HTN	13 (2.6)	217 (43.7)	201 (40.4)	62 (12.5)	4 (0.8)	
Non-HTN	29 (2.7)	363 (33.4)	476 (43.8)	202 (18.6)	18 (1.7)	
White bread						*
HTN	116 (23.3)	63 (12.7)	38 (7.6)	144 (28.9)	137 (27.5)	
Non-HTN	175 (16.1)	155 (14.3)	140 (12.9)	247 (22.8)	368 (33.9)	
Whole grain bread						*
HTN	224 (45.7)	62 (12.7)	38 (7.8)	94 (19.2)	72 (14.7)	
Non-HTN	556 (52.1)	196 (18.4)	76 (7.1)	138 (12.9)	101 (9.5)	
Rice and pasta						
HTN	18 (3.6)	271 (54.5)	16 3(32.8)	33 (6.6)	12 (2.4)	
Non-HTN	42 (3.9)	513 (48.2)	386 (36.3)	103 (9.7)	20 (1.9)	
Cooked vegetables						***
HTN	34 (6.8)	280 (56.1)	130 (26.1)	38 (7.6)	17 (3.4)	
Non-HTN	85 (7.8)	615 (56.7)	305 (28.1)	66 (6.1)	14 (1.3)	
Fruits						**
HTN	10 (2.0)	89 (17.8)	88 (17.6)	261 (52.1)	53 (10.6)	
Non-HTN	24 (2.2)	254 (23.4)	240 (22.1)	452 (41.6)	117 (10.8)	
Sweets						*
HTN	65 (13.2)	244 (49.5)	89 (18.1)	89 (18.1)	6 (1.2)	
Non-HTN	67 (6.2)	451 (41.6)	245 (22.6)	288 (26.5)	34 (3.1)	

Data are percent for categorical. *≤0.001, **≤0.01, ***≤0.05. HTN= Hypertension;

Components presumed to be detrimental: meat, fried potatoes or chips, sweets and fast food
Components presumed to be beneficial: raw vegetables, cooked vegetables, fruits, olive oil, grains, fish, rice and pasta, brown bread or crackers, white bread or crackers

Table 2: BDS-22 characteristics between patients with and without HTN:

Characteristic		All patients n(%)	*Patients with HTN*	*Patients without HTN*	*P value*
Number		2008 (100)	601 (30.2)	1388 (69.8%)	
Feel despaired	Never (0)	1416 (71.2)	406 (68.2)	999 (72.4)	0.026
	Little (1)	326 (16.4)	102 (17.1)	220 (16.0)	
	Moderate (2)	167 (8.4)	51 (8.6)	115 (8.3)	
	Much (3)	81 (4.1)	36 (6.1)	45 (3.3)	
Think life has no meaning	Never (0)	1596 (80.2)	452 (76.1)	1130 (81.9)	0.003
	Little (1)	202 (10.2)	74 (12.5)	126 (9.1)	
	Moderate (2)	110 (5.6)	32 (5.4)	78 (5.7)	
	Much (3)	82 (4.1)	36 (6.1)	45 (3.3)	
Feel empty	Never (0)	1357 (68.2)	372 (62.5)	974 (70.6)	<0.0001
	Little (1)	366 (18.4)	122 (20.5)	240 (17.4)	
	Moderate (2)	142 (7.1)	40 (6.7)	102 (7.4)	
	Much (3)	125 (6.3)	61 (10.3)	63 (4.6)	
Feel on the edge	Never (0)	1687 (84.8)	474 (79.7)	1198 (86.9)	<0.0001
	Little (1)	171 (3.6)	72 (12.1)	98 (7.1)	
	Moderate (2)	72 (3.6)	19 (3.2)	53 (3.8)	
	Much (3)	60 (3.0)	30 (5.0)	29 (2.1)	
Feel you don't recognize yourself	Never (0)	1724 (86.6)	508 (85.4)	1203 (87.2)	0.524
	Little (1)	146 (7.3)	48 (8.1)	94 (6.8)	
	Moderate (2)	67 (3.4)	24 (4.0)	43 (3.1)	
	Much (3)	54 (2.7)	15 (2.5)	39 (2.8)	
Isolate yourself	Never (0)	1439 (72.3)	408 (68.6)	1015 (73.6)	0.023
	Little (1)	359 (18.0)	113 (19.0)	245 (17.8)	
	Moderate (2)	116 (5.9)	41 (6.9)	76 (5.5)	
	Much (3)	76 (3.8)	33 (5.5)	43 (3.1)	
Lost the desire to learn	Never (0)	1442 (72.5)	373 (62.7)	1057 (76.6)	<0.0001
	Little (1)	229 (11.5)	88 (14.8)	140 (10.2)	
	Moderate (2)	161 (8.1)	55 (9.2)	107 (7.8)	
	Much (3)	158 (7.9)	79 (13.3)	75 (5.4)	
Lack enthusiasm	Never (0)	1385 (69.6)	397 (66.8)	976 (70.8)	<0.0001
	Little (1)	371 (18.6)	99 (16.7)	268 (19.4)	
	Moderate (2)	124 (6.2)	55 (9.3)	69 (5.0)	
	Much (3)	110 (5.5)	43 (7.2)	66 (4.8)	
I don't know what I want	Never (0)	1495 (75.1)	452 (76.1)	1029 (74.6)	0.904
	Little (1)	291 (14.6)	85 (14.3)	204 (14.8)	
	Moderate (2)	100 (5.0)	30 (5.1)	69 (5.0)	
	Much (3)	104 (5.2)	27 (4.5)	77 (5.6)	
Your ideas are puzzled	Never (0)	1206 (60.6)	364 (61.2)	833 (60.4)	0.828
	Little (1)	505 (25.4)	145 (24.4)	357 (25.9)	
	Moderate (2)	144 (7.2)	42 (7.1)	99 (7.2)	
	Much (3)	134 (6.8)	44 (7.4)	90 (6.5)	
You have constipation or diarrhea	Never (0)	1389 (69.8)	499 (67.1)	978 (70.9)	0.293
	Little (1)	357 (17.9)	121 (20.3)	235 (17.0)	
	Moderate (2)	157 (7.9)	46 (7.7)	107 (7.8)	
	Much (3)	88 (4.4)	29 (4.9)	59 (4.3)	
You have stomach cramps	Never (0)	1406 (70.6)	400 (67.2)	993 (72.0)	0.004
	Little (1)	375 (18.8)	118 (19.8)	256 (18.6)	
	Moderate (2)	109 (5.5)	48 (8.1)	58 (4.2)	
	Much (3)	100 (5.0)	29 (4.9)	72 (5.2)	
You have stomach heartburn	Never (0)	1270 (63.8)	360 (60.5)	898 (65.2)	<0.0001
	Little (1)	438 (22.0)	133 (22.4)	304 (22.1)	
	Moderate (2)	168 (8.4)	74 (12.4)	90 (6.5)	
	Much (3)	114 (5.7)	28 (4.7)	86 (6.2)	

You find it difficult to relax	Never (0)	1176 (58.6)	345 (58.0)	821 (59.5)	0.001
	Little (1)	497 (25.0)	127 (21.3)	364 (26.4)	
	Moderate (2)	181 (9.1)	74 (12.4)	107 (7.8)	
	Much (3)	137 (6.9)	49 (8.2)	87 (6.3)	
You get angry for ridiculous reasons	Never (0)	874 (43.9)	250 (42.0)	615 (44.6)	0.108
	Little (1)	571 (28.7)	167 (28.1)	400 (29.0)	
	Moderate (2)	230 (11.6)	85 (14.3)	144 (10.4)	
	Much (3)	315 (15.8)	93 (15.6)	219 (15.9)	
Your mood changes for tiny matters	Never (0)	957 (48.1)	308 (51.9)	640 (46.4)	0.162
	Little (1)	485 (24.4)	133 (22.4)	349 (25.3)	
	Moderate (2)	286 (14.4)	77 (13.0)	204 (14.8)	
	Much (3)	263 (13.2)	76 (12.8)	186 (13.5)	
You are in a bad mood	Never (0)	1284 (64.5)	389 (65.4)	885 (64.2)	0.400
	Little (1)	400 (20.1)	110 (18.5)	288 (20.9)	
	Moderate (2)	199 (10.0)	58 (9.7)	138 (10.0)	
	Much (3)	107 (5.4)	38 (6.4)	68 (4.9)	
You have memory troubles	Never (0)	1201 (60.3)	325 (54.7)	865 (62.8)	0.009
	Little (1)	481 (24.2)	165 (27.8)	311 (22.6)	
	Moderate (2)	181 (9.1)	59 (9.9)	121 (8.8)	
	Much (3)	128 (6.4)	45 (7.6)	81 (5.9)	
You have difficulty concentrating	Never (0)	1391 (69.9)	412 (69.5)	963 (69.9)	0.966
	Little (1)	425 (21.4)	127 (21.4)	297 (21.6)	
	Moderate (2)	118 (5.9)	38 (6.4)	80 (5.8)	
	Much (3)	55 (2.8)	16 (2.7)	38 (2.8)	
You don't know what values to adopt	Never (0)	1694 (85.7)	504 (84.7)	1174 (85.9)	0.882
	Little (1)	185 (9.4)	60 (10.1)	125 (9.2)	
	Moderate (2)	50 (2.5)	15 (2.5)	35 (2.6)	
	Much (3)	48 (2.4)	16 (2.7)	32 (2.3)	
You have panic attacks.	Never (0)	1654 (83.2)	479 (80.5)	1159 (84.2)	0.044
	Little (1)	205 (10.3)	63 (10.6)	142 (10.3)	
	Moderate (2)	66 (3.3)	28 (4.7)	38 (2.8)	
	Much (3)	63 (3.2)	25 (4.2)	38 (2.8)	
You worry about little things	Never (0)	1172 (58.9)	337 (56.6)	829 (60.1)	0.034
	Little (1)	436 (21.9)	122 (20.5)	312 (22.6)	
	Moderate (2)	170 (8.6)	61 (10.3)	103 (7.5)	
	Much (3)	212 (10.6)	75 (12.6)	135 (9.8)	
BDS-22 Score	Mean (SD) [min-max]	32.5 (11.1) [1-66]	33.5 (11.5) [1-66]	32.1 (10.8) [2-66]	0.010
	Male	31.2 (10.7) [2-66]	31.9 (10.5)	30.9 (10.8)	0.180
	Female	33.8 (11.2) [1-66]	35.7 (12.4)	33.1 (10.7)	0.004
	P value	<0.0001	<0.0001	<0.0001	

HTN= Hypertension; Beirut Distress Scale (BDS-22). Possible scores range from 0 to 66 (maximum psychological distress)

Appendix 5

Additional and supplementary results from article 2

Table 1. Association between prevalent hypertension and the number of unhealthy behaviors in men using mPNNS

Term	*Model 1*	*P value*	*Model 2*	*P value*
mPNNS-GS		**0.0002**		**0.00013**
High	1.00 (ref)	-	1.00 (ref)	
Medium	1.14 [1.02-1.29]	0.0260	1.15 [1.02-1.29]	0.0215
Low	1.25 [1.10-1.29]	0.0004	1.24 [1.09-1.41]	0.0006
Low/medium vs. high	1.18 [1.05-1.32]	0.0059	1.18 [1.05-1.33]	0.0057
Physical activity		**<0.0001**		**<0.0001**
Sedentary	1.00 (ref)	-	1.00 (ref)	
Moderate	0.86 [0.78-0.95]	0.0037	0.88 [0.79-0.97]	0.0122
High	0.76 [0.69-0.84]	<0.0001	0.80 [0.72-0.88]	<0.0001
Moderate/high vs. sedentary	0.81 [0.74-0.89]	<0.0001	0.83 [0.76-0.92]	0.0002
BMI		**<0.0001**		**<0.0001**
<25	1.00 (ref)	-	1.00 (ref)	
25.0-29.9	2.03 [1.90-2.16]	<0.0001	1.95 [1.83-2.08]	<0.0001
≥30.0	4.19 [3.81-4.61]	<0.0001	3.80 [3.45-4.20]	<0.0001
≥25 vs. <25	2.39 [2.25-2.54]	<0.0001	2.26 [2.13-2.40]	<0.0001
Alcohol consumption		**<0.0001**		**<0.0001**
Never/light	1.00 (ref)	-	1.00 (ref)	
Moderate	0.99 [0.93-1.07]	0.94	0.99 [0.93-1.06]	0.9740
Heavy	1.43 [1.30-1.57]	<0.0001	1.39 [1.27-1.52]	<0.0001
Heavy vs. moderate/never	1.43 [1.32-1.55]	<0.0001	1.40 [1.30-1.52]	<0.0001
Nb. of unhealthy behaviors		**<0.0001**		**<0.0001**
0	1.00 (ref)	-	1.00 (ref)	
1	1.14 [0.96-1.37]	0.1374	1.13 [0.95-1.36]	0.1616
2	2.18 [1.83-2.61]	<0.0001	2.08 [1.75-2.49]	<0.0001
3 or more	3.17 [2.63-3.83]	<0.0001	2.93 [2.43-3.54]	<0.0001

Abbreviations: BMI, body mass index (Kg/m^2); mPNNS: modified Programme National Nutrition Sante Guideline Score

Model 1: logistic regression model adjusted for age, education level, monthly income and antihypertensive medications

Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, hypercholesterolemia, and antihypertensive medications

Table 2. Association between prevalent hypertension and the number of unhealthy behaviors in women using mPNNS

Term	*Model 1*	*P value*	*Model 2*	*P value*
mPNNS-score		**0.0078**		**0.0131**
High	1.00 (ref)		1.00 (ref)	
Medium	1.14 [1.02-1.27]	0.0164	1.14 [1.02-1.27]	0.0225
Low	1.21 [1.02-1.27]	0.0013	1.19 [1.06-1.35]	0.0033
Low/medium vs. high	1.16 [1.05-1.29]	0.0056	1.15 [1.03-1.28]	0.0095
Physical activity		**<0.0001**		**<0.0001**
Sedentary	1.00 (ref)		1.00 (ref)	
Moderate	0.90 [0.79-1.02]	0.1023	0.91 [0.81-1.03]	0.1620
High	0.78 [0.69-0.88]	<0.0001	0.81 [0.72-0.91]	0.0006
Moderate/high vs. sedentary	0.83 [0.74-0.93]	0.0024	0.85 [0.76-0.96]	0.0086
BMI		**<0.0001**		**<0.0001**
<25	1.00 (ref)		1.00 (ref)	
25.0-29.9	1.65 [1.52-1.77]	<0.0001	1.60 [1.49-1.73]	<0.0001
≥30.0	3.82 [3.47-4.20]	<0.0001	3.59 [3.26-3.95]	<0.0001
≥25 vs. <25	2.18 [2.04-2.33]	<0.0001	2.08 [1.95-2.23]	<0.0001
Alcohol consumption		**<0.0001**		**<0.0001**
Never/light	1.00 (ref)		1.00 (ref)	
Moderate	0.83 [0.78-0.89]	<0.0001	0.85 [0.79-0.91]	<0.0001
Heavy	1.07 [0.95-1.19]	0.2481	1.07 [0.95-1.19]	0.2581
Heavy vs. moderate/never	1.17 [1.05-1.30]	0.0040	1.16 [1.04-1.29]	0.0067
Nb. of unhealthy behaviors		**<0.0001**		**<0.0001**
0	1.00 (ref)		1.00 (ref)	
1	1.15 [1.01-1.34]	0.0466	1.15 [0.99-1.34]	0.0513
2	2.06 [1.78-2.39]	<0.0001	1.98 [1.71-2.30]	<0.0001
3 or more	2.61 [2.18-3.11]	<0.0001	2.46 [2.06-2.95]	<0.0001

Abbreviations: BMI, body mass index (Kg/m^2); mPNNS: modified Programme National Nutrition Sante Guideline Score

Model 1: logistic regression model adjusted for age, education level, monthly income and antihypertensive medications

Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, hypercholesterolemia, and antihypertensive medications

Appendix 6

Additional and supplementary results from article 3

Table 1. Association between uncontrolled hypertension and the number of unhealthy behaviors in women

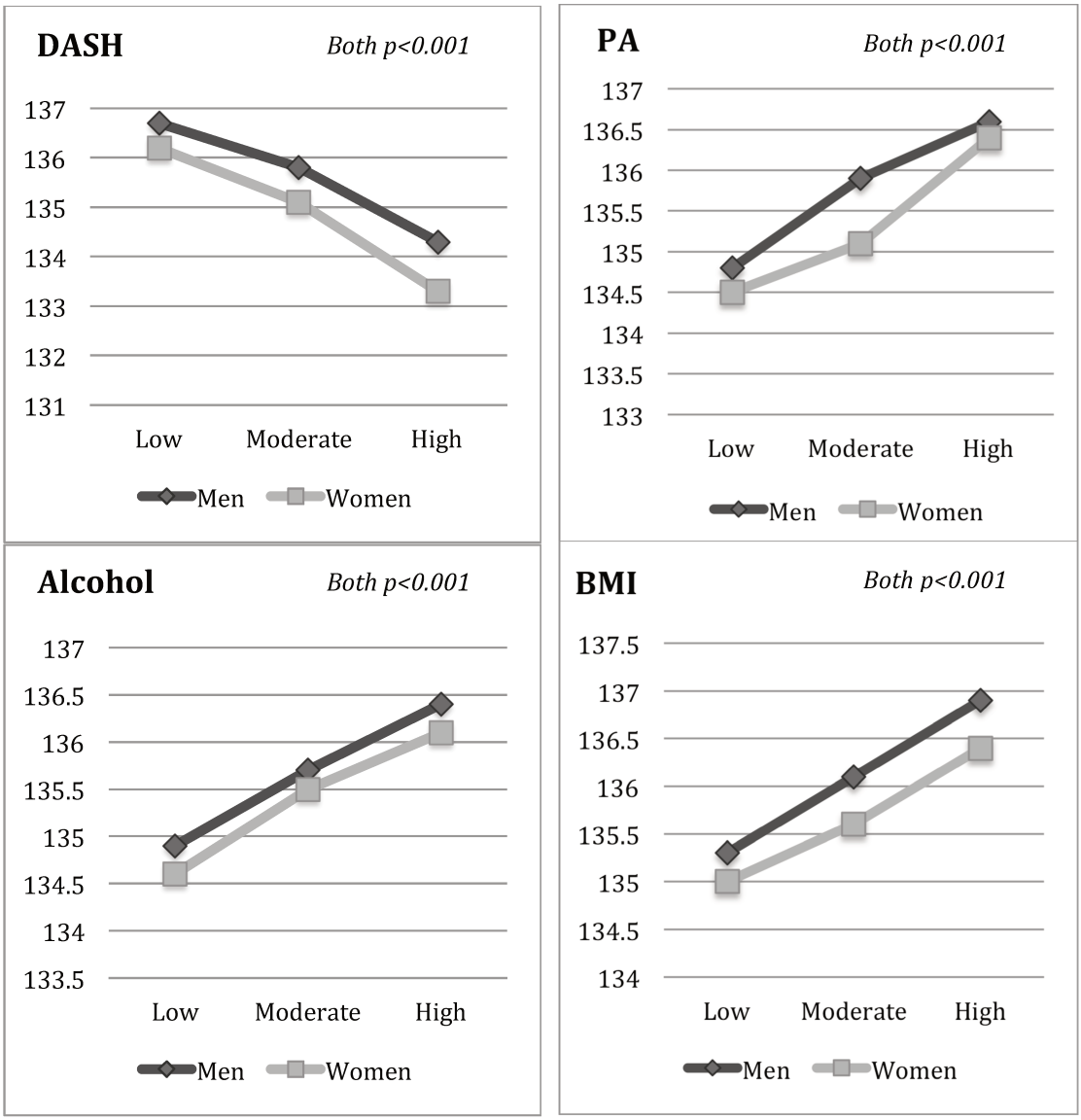
Term	*Model 1*	*P value*	*Model 2*	*P value*
DASH		**0.222**		**0.223**
High	1.00 (ref)	-	1.00 (ref)	-
Medium	1.17 [0.91-1.50]	0.233	1.15 [0.89-1.49]	0.277
Low	1.19 [0.98-1.46]	0.083	1.19 [0.98-1.46]	0.085
Low/medium vs. high	1.01 [0.84-1.20]	0.972	1.01 [0.85-1.21]	0.863
Physical activity		**0.118**		**0.147**
High	1.00 (ref)	-	1.00 (ref)	-
Moderate	1.14 [1.01-1.29]	0.046	1.13 [0.99-1.28]	0.063
Sedentary	0.99 [0.80-1.23]	0.972	0.99 [0.79-1.22]	0.893
Moderate/sedentary vs. high	1.10 [0.98-1.25]	0.092	1.09 [0.97-1.24]	0.124
BMI		**0.701**		**0.608**
<25	1.00 (ref)	-	1.00 (ref)	-
25.0-29.9	1.06 [0.92-1.22]	0.436	1.04 [0.90-1.19]	0.614
≥30.0	1.01 [0.87-1.16]	0.938	0.96 [0.82-1.12]	0.600
≥25 vs. <25	1.03 [0.91-1.17]	0.603	1.01 [0.88-1.14]	0.968
Alcohol consumption		**0.502**		**0.512**
Never/light	1.00 (ref)	-	1.00 (ref)	-
Moderate	1.02 [0.89-1.18]	0.755	1.03 [0.89-1.19]	0.664
Heavy	1.14 [0.91-1.44]	0.252	1.15 [0.91-1.44]	0.250
Heavy vs. moderate/never	1.12 [0.91-1.38]	0.257	1.12 [0.92-1.37]	0.284
Nb. of unhealthy behaviors		**0.267**		**0.314**
0	1.00 (ref)	-	1.00 (ref)	-
1	1.34 [0.96-1.89]	0.090	1.34 [0.96-1.89]	0.088
2	1.33 [0.95-1.86]	0.094	1.30 [0.93-1.83]	0.124
3 or more	1.45 [1.01-2.11]	0.047	1.40 [0.97-2.05]	0.070

Abbreviations: BMI, body mass index (Kg/m^2); DASH, dietary approach to stop hypertension
Model 1: logistic regression model adjusted for age, education level, monthly income.
Model 2: logistic regression model adjusted for age, education level, monthly income, diabetes, and dyslipidemia.

Appendix 7

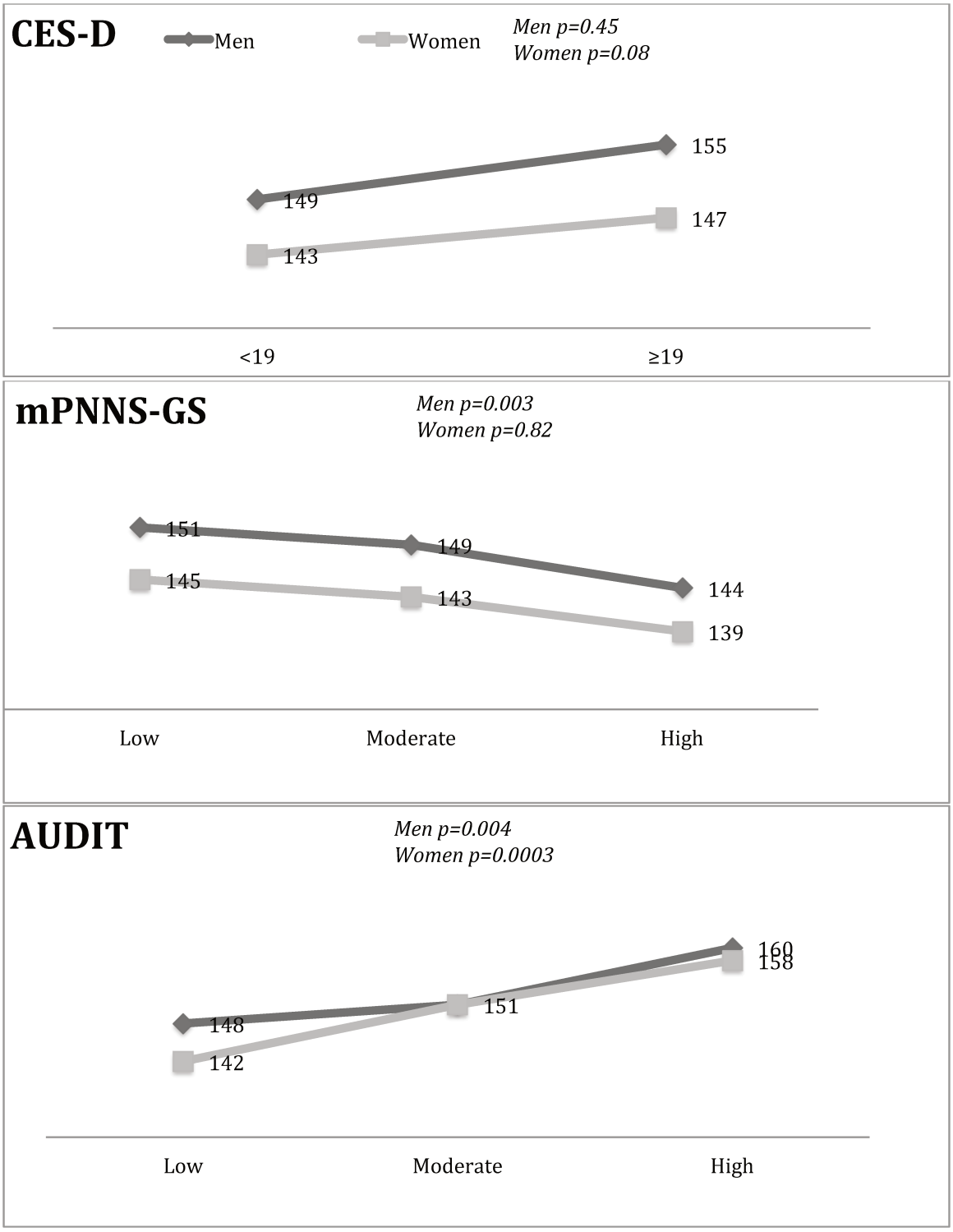
Additional and supplementary results from article 4

Figure 1. Age-adjusted mean SBP among studied factors by gender.



Abbreviations: BMI: Body mass index (Kg/m^2); DASH, dietary approach to stop hypertension; SBP: Systolic blood pressure; PA: Physical activity.

Figure 2. Age-adjusted mean SBP among other variables of interest



Abbreviations: AUDIT: Alcohol Use DIsorders Test; CES-D: Center of Epidemiologic Studies Depression scale; mPNNS-GS: modified National Program on Nutrition and Health-Guideline Score

Table 1. Age adjusted association between patients' characteristics and uncontrolled blood pressure in women.

Characteristic	*Uncontrolled*	*Controlled*	**P value*
Number (%)	**2227 (37.1)**	**2451 (52.1)**	
Age (years)	61.2±7.5	57.6±9.8	<0.001
Duration of Hypertension	4.8±10.6	5.7±11.5	<0.001
Systolic BP	153.9±12.7	126.0±9.2	<0.001
Diastolic BP	85.5±9.1	74.8±7.3	<0.001
BMI (Kg/m^2)	27.7±5.6	27.6±5.7	<0.001
BMI class			<0.001
≤25	815 (36.6)	949 (38.7)	
25.1-29.9	745 (33.4)	764 (31.2)	
≤25	667 (30.0)	738 (30.1)	0.005
Familial situation			
Single	645 (29.0)	750 (30.6)	
Couple life	1582 (71.0)	1701 (69.4)	
Educational level			<0.001
≤ high school diploma	1042 (46.8)	983 (40.1)	
Undergraduate degree	378 (17.0)	450 (18.4)	
Postgraduate degree	807 (36.2)	1018 (41.5)	
Income of the house/month			0.240
Less than 1000 €	119 (5.3)	126 (5.1)	
1000 – 2099 €	561 (25.2)	576 (23.5)	
2100 – 4199 €	1074 (48.2)	1255 (51.2)	
More or equal than 4200 €	473 (21.2)	494 (20.2)	
Smoking status			<0.001
Non-smoker	1396 (62.7)	1379 (56.3)	
Previous smoker	647 (29.1)	754 (30.8)	
Current smoker	184 (8.3)	318 (13.0)	
Smoking pack-years			
Alcohol (g/day)	0.8±1.2	0.7±1.0	<0.001
Alcohol consumption			<0.001
Never/light	504 (22.6)	598 (24.4)	
Moderate	1500 (67.4)	1644 (67.1)	
Heavy	223 (10.0)	209 (8.5)	
Physical activity			0.334
Sedentary (1-2)	567 (25.5)	668 (27.3)	
Moderate physical activity (3)	942 (42.3)	1042 (42.5)	
High physical activity (4-6)	718 (32.2)	741 (30.2)	
DASH categories			0.122
Low	265 (11.9)	332 (13.6)	
Medium	1755 (78.8)	1871 (76.3)	
High	207 (9.3)	248 (10.1)	
Glycemia	5.7±1.3	5.5±1.1	
Total Chol	5.9±1.1	5.7±1.0	
HDL	1.7±0.4	1.6±0.4	
TG	1.3±0.7	1.2±0.7	
History of CV events	127 (5.7)	175 (7.1)	<0.001

DM	261 (11.7)	232 (9.5)	0.012
Dyslipidemia	1263 (56.7)	1196 (48.8)	<0.001
Chronic kidney disease	33 (1.5)	30 (1.2)	0.446

Data are mean ±SD for quantitative variables or percent for categorical.
**P* from logistic regression model adjusted for age and sex.
Abbreviations: BMI: Body mass index (Kg/m^2); BP: Blood pressure; CI: confidence interval; CV: Cardiovascular; DASH, dietary approach to stop hypertension; DM: Diabetes mellitus; HDL: High density lipoproteins; ORa: adjusted odds ration; SD: standard deviation; TG: Triglycerides;

Table 2. Age adjusted association between patients' characteristics and uncontrolled blood pressure in men.

Characteristic	*Uncontrolled*	*Controlled*	**P value*
Number (%)	**3776 (62.9)**	**2256 (47.9)**	
Age (years)	60.9±7.8	58.9±8.7	<0.0001
Duration of Hypertension	13.0±19.0	12.9±18.5	<0.0001
Systolic BP	154.7±12.7	129.1±7.8	<0.0001
Diastolic BP	87.5±8.8	76.4±7.0	<0.0001
BMI (Kg/m^2)	28.6±4.4	27.9±4.3	<0.0001
BMI class			<0.0001
≤25	755 (20.0)	586 (26.0)	
25.1-29.9	1784 (47.3)	1070 (47.4)	
≤25	1237 (32.8)	600 (26.6)	
Familial situation			0.0005
Single	674 (17.9)	485 (21.5)	
Couple life	3102 (82.2)	1771 (78.5)	
Educational level			<0.0001
≤ high school diploma	1770 (46.9)	959 (42.5)	
Undergraduate degree	569 (15.1)	296 (13.1)	
Postgraduate degree	1437 (38.1)	1001 (44.4)	
Income of the house/month			0.0026
Less than 1000 €	150 (4.0)	109 (4.8)	
1000 – 2099 €	718 (19.0)	432 (19.2)	
2100 – 4199 €	1861 (49.3)	1011 (44.8)	
More or equal than 4200 €	1047 (27.7)	704 (31.2)	
Smoking status			<0.0001
Non-smoker	1344 (35.6)	868 (38.5)	
Previous smoker	2032 (53.8)	1090 (48.3)	
Current smoker	400 (10.6)	298 (13.2)	
Alcohol (g/day)	1.9±2.2	1.7±2.0	<0.0001
Alcohol consumption			<0.0001
Never/light	427 (11.3)	299 (13.3)	
Moderate	2553 (67.6)	1574 (69.8)	
Heavy	796 (21.1)	383 (17.0)	
Physical activity			0.0001
Sedentary (1-2)	1107 (29.3)	740 (32.8)	
Moderate physical activity (3)	1574 (41.7)	949 (42.1)	
High physical activity (4-6)	1095 (29.0)	567 (25.1)	
DASH categories			0.1143
Low	485 (12.8)	279 (12.4)	
Medium	3011 (79.7)	1776 (78.7)	
High	280 (7.4)	201 (8.9)	
Glycemia	6.2±1.5	6.0±1.4	
Total Chol	5.3±1.0	5.1±1.1	
HDL	1.3±0.3	1.3±0.3	
TG	1.6±0.9	1.4±0.9	
History of CV events	582 (15.4)	517 (22.9)	<0.0001

DM	784 (20.8)	384 (17.0)	0.0003
Dyslipidemia	2470 (65.4)	1489 (66.0)	0.6413
Chronic kidney disease	67 (1.8)	48 (2.1)	0.3349

Data are mean ±SD for quantitative variables or percent for categorical.
**P* from logistic regression model adjusted for age and sex.
Abbreviations: BMI: Body mass index (Kg/m^2); BP: Blood pressure; CI: confidence interval; CV: Cardiovascular; DASH, dietary approach to stop hypertension; DM: Diabetes mellitus; HDL: High density lipoproteins; ORa: adjusted odds ration; SD: standard deviation; TG: Triglycerides;