Alma Mater Studiorum - Università di Bologna

DOTTORATO DI RICERCA IN

PSICOLOGIA

Ciclo 34

**Settore Concorsuale:** 11/E4 - PSICOLOGIA CLINICA E DINAMICA

**Settore Scientifico Disciplinare:** M-PSI/08 - PSICOLOGIA CLINICA

# PSYCHOLOGICAL CHARACTERIZATION OF HYPERTENSIVE PATIENTS: ASSOCIATIONS WITH ADHERENCE TO PHARMACOLOGICAL TREATMENT AND SELF-MANAGEMENT

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**Esame finale anno 2022**

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## Abstract

**Introduction:** The role of psychosocial factors in the onset and progression of essential hypertension has been object of a large body of literature, yet research findings appear to be rather controversial, particularly in terms of their implications for clinical management.

**Aims:** We introduced some novel approaches and conducted two studies in order to assess the predictive role of psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, well-being and quality of life on adherence to antihypertensive medications, lifestyle behaviors, hypertension severity and absolute cardiovascular risk grading, as well as their temporal stability at 1-year follow-up, in a sample of hypertensive patients. We expected to find a specific psychological characterization of hypertensive patients compared to normotensive controls. In addition, we aimed to validate the Italian version of the Hong Psychological Reactance Scale (HPRS).

**Methods:** Eighty consecutive outpatients with essential hypertension treated with antihypertensive medications (47.5% females, mean age 55.23 ± 9.48 years, age range 22-69) were compared to 80 normotensive matched controls. Psychosocial variables were assessed using clinical interviews and self-rating questionnaires at baseline and at 1-year follow-up. Cardiac parameters were also collected. As to the validation study of the HPRS, data were provided by 150 individuals from general population (54.7% females, mean age 51.6 ± 13.04 years, age range 18-75).

**Results:** Hypertensive patients reported significantly higher levels of psychological distress and lower levels of psychological well-being ($p < .05$) at baseline compared to controls. Among hypertensive patients, allostatic overload (AO) was the most frequently reported psychosomatic syndrome at baseline (42.5%). Further, patients with AO displayed significantly greater levels of psychological distress ($p < .05$) and lower levels of well-being and quality of life ($p < .05$) than those without. Regression analyses revealed that hypertensive patients with illness denial were more likely to report poor adherence to pharmacological treatment. Moreover, hypertensive patients with illness denial and those with higher levels of affective symptomatology were significantly less likely to follow a balanced diet. At 1-year follow-up, hypertensive patients displayed significantly higher levels of psychological well-being ($p < .001$) as well as significantly lower levels of stress, mental pain and quality of life ($p < .05$).

**Conclusions:** These findings suggest the clinical relevance of psychosocial factors and psychosomatic syndromes in the progression and prognosis of hypertension, with important clinical implications for its pharmacological and non-pharmacological management. As to the Italian validation of the HPRS, results support previous research findings, even though a confirmatory factor analysis should be carried out.

## Chapter 1. Epidemiological and clinical characteristics of essential hypertension

### 1.1 Definition and prevalence

According to the most recent guidelines (Williams et al., 2018), hypertension is defined as the level of blood pressure at which treatment benefits outweigh treatment risks. Particularly, hypertension is an asymptomatic condition characterized by systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHG (Williams et al., 2018). This classification is used for younger (from 16 years), middle-aged adults and older individuals, supporting the definition of hypertension provided in the previous guidelines (**Table 1**) (Mancia et al., 2007, 2013).

**Table 1**. Classification of office blood pressure and hypertension grade

| Category | Systolic (mmHg) | | Diastolic (mmHg) |
|---|---|---|---|
| Optimal | <120 | and | <80 |
| Normal | 120–129 | and/or | 80–84 |
| High normal | 130–139 | and/or | 85–89 |
| Grade 1 hypertension | 140–159 | and/or | 90–99 |
| Grade 2 hypertension | 160–179 | and/or | 100–109 |
| Grade 3 hypertension | ≥180 | and/or | ≥110 |
| Isolated systolic hypertension[b] | ≥140 | and | <90 |

Globally, an estimated 1.28 billion adults aged 30-79 years have hypertension (WHO, 2021), but this trend is increasing over time, in particular among elderly individuals (Chow et al., 2013; Prince et al., 2012). It is estimated that the prevalence of individuals with essential hypertension will increase by 20% by 2025 (Kearney et al., 2005). Further, high prevalence rates appear to be consistent among different countries and uncorrelated with some sociodemographic variables, such as income level (Chow et al., 2013).

1.2 Blood pressure measurement

Regarding conventional office blood pressure measurements, the most frequently used instruments include auscultatory or oscillometric semiautomatic or automatic sphygmomanometers (Stergiou et al., 2018). Blood pressure values should be measured in a quiet and comfortable environment using an adequate cuff size – usually with a standard bladder cuff 13cm wide and 35cm long - for both arms circumferences (Williams et al., 2018). Further, measurements should be repeated in order to detect a possible condition of orthostatic hypotension and should be recorded to perform additional measurements if necessary (i.e., if the first two readings differ by <10mmHg, unstable blood pressure values) (Williams et al., 2018).

Out of office blood pressure measurement is performed using either home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM). These strategies provide a larger number of measurements in conditions that seem to be more representative of daily life (**Table 2**).

**Table 2**. Hypertension definitions according to office, ambulatory, and home blood pressure levels

| Category | SBP (mmHg) | | DBP (mmHg) |
|---|---|---|---|
| Office BP[a] | ≥140 | and/or | ≥90 |
| Ambulatory BP | | | |
| Daytime (or awake) mean | ≥135 | and/or | ≥85 |
| Night-time (or asleep) mean | ≥120 | and/or | ≥70 |
| 24 h mean | ≥130 | and/or | ≥80 |
| Home BP mean | ≥135 | and/or | ≥85 |

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure
(Williams et al., 2018)

Home blood pressure is defined as the average of all blood pressure readings, adequately performed for at least three days, in the morning and the evening in a quiet environment after five minutes of rest (Parati et al., 2008). HBPM values tend to be lower and to better predict cardiovascular morbidity and mortality in comparison to office blood pressure values (Ward et al., 2012).

ABPM is the average of blood pressure readings over a specific period of time, usually of 24 hours. This strategy is used to record blood pressure values at 15-30 minutes intervals, during the day, night and at 24 hours. Similarly to HBPM, ABPM values are lower than office blood pressure values (Williams et al., 2018) and represent good predictors of hypertension-mediated organ damage (HMOD; Gaborieau et al., 2008) as well as coronary morbid or fatal events and stroke (Fagard et al., 2008; Parati et al., 2016; Piper et al., 2015) compared to office blood pressure. Main advantages and disadvantages of ABPM and HBPM are displayed in **Table 3**.

Since hypertension is mainly an asymptomatic condition, structured screening programs and occasional blood pressure measurements have a central role in its detection. Undertaking these programs could lead to unawareness (Chow et al., 2013; Lindholt & Sogaart, 2017) and greater rates of undetected hypertension (Williams et al., 2018). Therefore, is recommended to take part to screening programs regularly depending on individual blood pressure levels. According to the most recent guidelines for the management of arterial hypertension (Williams et al., 2018), healthy individuals with an optimal blood pressure should monitor its values every five years whereas individuals with normal blood pressure should measure it every three years. Patients with high-normal blood pressure should record it every year since values of 130-139/85-89mmHg tend to progressively increase over time.

**Table 3.** Advantages and disadvantages of ABPM and HBPM

| ABPM | HBPM |
|---|---|
| **Advantages**<br>• Can identify white-coat and masked hypertension<br>• Stronger prognostic evidence<br>• Night-time readings<br>• Measurement in real-life settings<br>• Additional prognostic BP phenotypes<br>• Abundant information from a single measurement session, including short-term BP variability | **Advantages**<br>• Can identify white-coat and masked hypertension<br>• Cheap and widely available<br>• Measurement in a home setting, which may be more relaxed than the doctor's office<br>• Patient engagement in BP measurement<br>• Easily repeated and used over longer periods to assess day-to-day BP variability |
| **Disadvantages**<br>• Expensive and sometimes limited availability<br>• Can be uncomfortable | **Disadvantages**<br>• Only static BP is available<br>• Potential for measurement error<br>• No nocturnal readings[a] |

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; HBPM: home blood pressure monitoring
(Williams et al., 2018)

### 1.3 Cardiovascular risk assessment and hypertension-mediated organ damage

Elevated blood pressure levels accounts for high rates of disability and mortality (Forouzanfar et al., 2017) and were found to have independent and continuous associations with the incidence of several cardiovascular and renal diseases (Lewington et al., 2002; Lip et al., 2017). The role of blood pressure in relation to the greater risk of cardiovascular events has been widely recognized (Lip et al., 2017; Williams et al., 2018) at all ages (Vishram et al., 2012) and all ethnic groups (Brown et al., 2007; Lawes et al., 2003). Further, according to literature, after the age of 50 years systolic blood pressure seems to be a better predictor of events than diastolic blood pressure (Franklin et al., 1999; Vishram et al., 2012; Williams & Lindholm, 2008), whereas in younger individuals (<50 years) diastolic blood pressure appears to be more frequently related to a greater cardiovascular risk (Franklin et al., 1999).

Cardiovascular risk in hypertensive patients was found to be influenced by several sociodemographic characteristics (i.e., sex, age, psychosocial and socioeconomic factors) as well as biological parameters, such as total and HDL cholesterol, uric acid, BMI and heart rate (Williams et al., 2018). Furthermore, diabetes, early onset menopause, family history of early onset hypertension or premature cardiovascular diseases, represent relevant factors influencing cardiovascular risk in patients with hypertension (Williams et al., 2018).

The total cardiovascular risk is defined as the likelihood of developing a cardiovascular event over a defined period (Williams et al., 2018). One of the most frequently used cardiovascular risk assessment systems is the Systematic COronary Risk Evaluation (SCORE). The SCORE is based on representative European cohort data sets estimating the 10-year risk of a first fatal atherosclerotic event, in relation to age, sex, smoking habits, total cholesterol level and systolic blood pressure levels (Aktas et al., 2004; Williams et al., 2018). The Systematic COronary Risk Evaluation system includes several risk categories (**Table 4**) and appears to be a useful tool in order to prevent and rapidly assess possible future cardiovascular events.

**Table 4.** SCORE cardiovascular risk categories

| | |
|---|---|
| **Very high risk** | People with any of the following: |
| | **Documented CVD, either clinical or unequivocal on imaging.**<br>• **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD<br>• **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥ 50% stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness<br>• **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia<br>• **Severe CKD** (eGFR < 30 mL/min/1.73 $m^2$)<br>• **A calculated 10 year SCORE of ≥ 10%** |
| **High risk** | People with any of the following:<br>• **Marked elevation of a single risk factor**, particularly cholesterol > 8 mmol/L (> 310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP ≥ 180/110 mmHg)<br>• **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk) |
| | **Hypertensive LVH** |
| | **Moderate CKD (eGFR 30-59 mL/min/1.73 $m^2$)** |
| | **A calculated 10 year SCORE of 5-10 %** |
| **Moderate risk** | People with:<br>• **A calculated 10 year SCORE of ≥ 1 to <5%**<br>• **Grade 2 hypertension**<br>• **Many middle-aged people belong to this category** |
| **Low risk** | People with:<br>• **A calculated 10 year SCORE of < 1%** |

BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; LVH: left ventricular hypertrophy; TIA: transient ischaemic attack; PAD: peripheral artery disease; SCORE: Systematic COronary Risk Evaluation (Williams et al., 2018)

However, the SCORE system only estimates the risk of fatal cardiovascular events and does not include all the HMOD features (Williams et al., 2018). Consequently, the use of SCORE should be followed by the assessment of the hypertension-mediated organ damage which is characterized by a relevant prognostic significance, particularly in hypertension.

HMOD represents the hypertension-induced structural and/or functional changes in major organs caused by elevated values of blood pressure (Williams et al., 2018). It is considered a relevant marker for preclinical and asymptomatic cardiovascular diseases (Devereux & Alderman, 1993) while multiple HMODs appear to increase the risk of several cardiovascular events (Cordero et al., 2011; Cuspidi et al., 2008; Greve et al., 2015; Mancia et al., 2007; Pontremoli et al., 1999; Roman et al., 1995). Furthermore, the presence of HMOD, as well as comorbidities and other cardiovascular risk factors, may influence the progression of hypertension-associated disease stages (**Table 5**) (Williams et al., 2018).

**Table 5.** Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities

| **Hypertension disease staging** | **Other risk factors, HMOD, ordisease** | BP (mmHg) grading | | | |
|---|---|---|---|---|---|
| | | High normal SBP 130–139 DBP 85–89 | Grade 1 SBP 140–159 DBP 90–99 | Grade 2 SBP 160–179 DBP 100–109 | Grade 3 SBP≥180 or DBP≥110 |
| Stage 1 (uncomplicated) | No other risk factors | Low risk | Low risk | Moderate risk | High risk |
| | 1 or 2 risk factors | Low risk | Moderate risk | Moderate to high risk | High risk |
| | ≥ 3 risk factors | Low to Moderate risk | Moderate to high risk | High Risk | High risk |
| Stage 2 (asymptomatic disease) | HMOD, CKD grade 3, or diabetes mellitus without organ damage | Moderate to high risk | High risk | High risk | High to very high risk |
| Stage 3 (established disease) | Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage | Very high risk | Very high risk | Very high risk | Very high risk |

BP: blood pressure; CKD: chronic kidney disease; DBP: diastolic blood pressure; HMOD: hypertension-mediated organ damage; SBP: systolic blood pressure; SCORE: Systematic Coronary Risk Evaluation (Williams et al., 2018)

HMOD appears to be associated with several cardiovascular, renal and cerebrovascular diseases. Excessive ventricular workload in patients with hypertension can result in hypertrophy, impaired ventricular activity and increased risk of atrial fibrillation and heart failure (Williams et al., 2018). Further, hypertension has been widely studied in relation to chronic kidney disease, representing its second most important cause. Increased blood pressure levels are also associated with brain damage, particularly ischaemic attacks and strokes (Williams et al., 2018).

Therefore, the HMOD assessment seems to be crucial. Screening tests for hypertension-mediated organ damage are usually divided in basic and more detailed tests. Basic screening tests include

ECG, urine albumin-creatinine ratio, blood creatinine, estimated glomerular filtration rate, and fundoscopy. These tests allow to detect possible cardiac abnormalities, such as ventricular hypertrophy and renal diseases (Williams et al., 2018). However, in particular cases, advanced HMOD screening tests, including echocardiography, carotid ultrasounds, Doppler studies, pulse wave velocity, ankle-brachial index, cognitive function tests and brain imaging, are highly recommended.

## 1.4 Risk and protective factors

A considerable progress has been made in studying epidemiological aspects related to essential hypertension and a number of studies demonstrated the importance of an adequate treatment in order to reduce mortality and disability rates due to high blood pressure (Ettehad et al., 2016; Rapsomaniki et al., 2014; Thomopoulos et al., 2014; Tsai et al., 2017; Yusuf et al., 2004). However, hypertension remains one of the major causes of cardiovascular diseases and mortality rates worldwide (Banegas et al., 2011; Chow et al., 2013; Falaschetti et al., 2014; Tocci et al., 2012; WHO, 2021).

High blood pressure prevalence tends to increase with age in both males and females (Singh et al., 2012). Men generally have higher BP at younger ages, whereas blood pressure values increase per decade is higher in women. Further, by the age of 60 years, women report a higher mean BP levels and greater hypertension prevalence rates than men (Mills et al., 2020).

Risk factors for excessive blood pressure levels should be considered as indicators of the probability that essential hypertension may occur. Nonetheless, risk factors have a prognostic role, influencing both the onset and prognosis of hypertension. Several risk prediction models for hypertension, taking into account anthropometric indexes and lifestyle-related factors, have been developed in several populations (Bozorgmanesh et al., 2011; Chien et al., 2011; Choi et al., 2014; Fava et al., 2013; Li et al., 2019; Lim et al., 2013, 2015; Lu et al., 2015; Otsuka et al., 2015; Niiranen et al., 2016; Parick et al., 2008). For instance, several sociodemographic characteristics, particularly ethnicity (Dorans et al., 2018), represent significant risk factors for hypertension (WHO, 2021). Further, lifestyle habits, defined as modifiable risk factors, have been shown to have a role in the onset and longitudinal course of essential hypertension (Mills et al., 2020; Williams et al., 2018).

Thus, a rapid and correct identification of risk factors seems to be essential in order to prevent hypertension and its consequences.

### 1.4.1 Sociodemographic characteristics

Several sociodemographic characteristics have been associated to a diagnosis of hypertension (Liew et al., 2019; Meng et al., 2011; WHO, 2021; Williams et al., 2018).

According to the most recent guidelines for hypertension management (Williams et al., 2018), the prevalence of hypertension increases with age, with rates varying from 60 to 75% for patients with 60 and 75 years, respectively. In a study conducted by Shen and colleagues (2017) on a sample of 4198 adults, age was found to be a risk factor for both hypertension and prehypertension. However, elevated levels of diastolic blood pressure and isolated diastolic hypertension seem to be more common in younger patients (Sundstrom et al., 2015). Further, individuals with less than 50 years have a greater likelihood of detecting secondary hypertension and tend to be more exposed to long-term risk of cardiovascular events and mortality with blood pressure levels greater than 130/80mmHg (Sundstrom et al., 2011; Williams, 2011).

As to gender, there are significant differences in prevalence, awareness, treatment and control rates of hypertension between men and women (Kearney et al., 2005; Wang et al., 2018; Zhang & Moran, 2017). Nevertheless, these gender differences depend on other sociodemographic factors, such as age or ethnicity (Song et al., 2020). Particularly, while hypertension awareness and control rates seem to be higher among Chinese women (Wang et al., 2018; Zhang & Moran, 2017), hypertension incidence among men and women appear to be strictly related to age. As reported by Ramirez and Sullivan (2018), in the USA, hypertension incidence tends to be higher among men until 45 years. From 46 to 64 years men and women show similar incidence rates, while from 65 years hypertension prevalence seems to be greater among women (Ramirez & Sullivan, 2018).

Regarding ethnicity, hypertension appears to be more prevalent among American (Ferdinand & Townsend, 2012; Whelton et al., 2016) and European (Modesti et al., 2016) Black population, in comparison to non-Black individuals. Further, Shen and colleagues (2017) have found that Han Chinese ethnicity was a risk factor for hypertension in a large sample of workers. However, differences in hypertension prevalence among several ethnic groups should be interpreted with caution, since ethnic groups may differ with regard to socioeconomic status, cardiovascular risk (Agyemang et al., 2014; Kaufman et al., 1997), genetic factors (Ferdinand & Townsend, 2012) and antihypertensive pharmacological treatment (Mehanna et al., 2017).

A high educational level was found to be a protective factor for chronic diseases, including hypertension (Tirapani & Fernandes, 2019). Several studies (Carrillo-Larco et al., 2016; Gupta et al., 2012; Non et al., 2012) have shown that higher educational levels are associated with blood pressure reduction and a lower prevalence of hypertension in different countries. However, opposite results were also reported (Divney et al., 2019; Tareque et al., 2015). Divney and colleagues (2019), using data from the National Health and Nutrition Examination Survey (NHANES), conducted a large multi-ethnic study with the aim to evaluate hypertension prevalence in relation to acculturation levels, gender and ethnicity. Results showed that, regardless of ethnicity, individuals with a high acculturation level were more likely to report hypertension than individuals with lower acculturation levels (Divney et al., 2019).

As to socioeconomic status, the increasing prevalence of hypertension in adult individuals living in low and middle-income countries (WHO, 2021) as well as the correlation between income and occupational status with risk factors of cardiovascular diseases (Abeyta et al., 2012; Siegel et al., 2013) have been recognized. Several studies have shown that individuals with low socioeconomic status reported a higher risk of mortality due to non-communicable diseases, including high blood pressure (Di Cesare et al., 2013; Tirapani & Fernandes, 2019). Further, several job characteristics, including quick shift intervals (Cho et al., 2020), night work and frequent rotations (Ferguson et al., 2019) and long working hours (Trudel et al., 2020), were found to represent hypertension risk factors.

1.4.2 Clinical and genetic variables

Although hypertension is a heterogeneous disease with a multifactorial aetiology, clinical and genetic variables may play a role in its onset and progression. The available literature suggests that essential hypertension is often in comorbidity with several physical diseases (Baker & Wilcox, 2017; Drawz et al., 2016; Farsang et al., 2016; Laukkanen et al., 2014; Lip et al., 2017; Manolis et al., 2013; Rapsomaniki et al., 2014; Rossignol et al., 2015; Williams et al., 2018; Yusuf et al., 2004). Further, the presence of certain genes has been found to be associated with the course of essential hypertension (Burrello et al., 2017; Dominiczak et al., 2017; Song et al., 2020).

Several physical illnesses may represent risk factors for the development and worsening of essential hypertension. As to cardiovascular diseases, although essential hypertension may represent a major risk factor for numerous cardiac pathologies (Williams et al., 2018), this association seems to be bidirectional. As reported by Safar (2018), increased arterial stiffness has a relevant effect on pulse pressure and cardiovascular risk, particularly in hypertensive patients. Furthermore, the role of arterial stiffness, as well as peripheral resistance, as potential contributors to the development of essential hypertension was previously described (Din-Dzietham et al., 2004; Taherzadeh et al., 2010).

Other risk factors for high blood pressure are represented by metabolic diseases, such as diabetes (Shen et al., 2017), and the elevated concentration of uric acid in the blood (Bjornstad et al., 2019; Shen et al., 2017). Further, as reported by Almagro and colleagues (2020), chronic obstructive pulmonary disease (COPD) is frequently associated with essential hypertension. Particularly, hypertension seems to be the most common concurrent disorder among COPD patients (Finks et al., 2020), whom tend to show increased risk of arterial hypertension (Chen et al., 2015).

As to genetics, a family history of hypertension seems to be frequent in hypertensive patients, with rates of heritability that vary from 35 to 50% (Fagard et al., 1995; Luft, 2001). Further, family history of high blood pressure represents a common risk factor for the development of essential hypertension (Li et al., 2019; Shen et al., 2017; Song et al., 2020). However, although several studies (Warren et al., 2017) have identified 120 loci associated with blood pressure values regulation, these findings only explain the 3.5% of the trait variance. A single gene mutation could fully explain the pathogenesis of hypertension guiding the clinicians to the best treatment options, however these monogenic forms appear to be rare. Song and colleagues (2020) reported that the Methylenetetrahydrofolate reductase (MTHFR), a key enzyme of homocysteine metabolism, has a role in the prognosis of hypertension. Particularly, the polymorphism of the (MTHFR) C677T was found to be an independent risk factor for the severity of hypertension (Song et al., 2020).

Regarding genetic testing, the most recent guidelines (Williams et al., 2018) recommend genetic testing only for patients suspected to have a rare monogenic cause of secondary hypertension or for patients with phaeochromocytoma, whereas routine genetic testing is not recommended.

### 1.4.3 Lifestyle habits

Lifestyle habits represent behavioral factors that are associated with and may contribute to high blood pressure levels (Mills et al., 2020; Williams et al., 2018).

As to dietary habits, diets and related trends are very heterogeneous across world regions, with clear differences between high- and low-income countries. Several studies have investigated the association between dietary patterns and hypertension. The DASH trial (Appel et al., 1997), demonstrated that a diet rich in fruit, vegetables and including low-fat dairy products with a total and saturated fat content lower than the typical US diet, reduced BP levels in both hypertensive patients and normotensive individuals. Further, also Vegetarian and Mediterranean dietary patterns, characterized by absent or rare meat consumption, moderate fat intake and high vegetables consumption, are associated with BP reduction (Nordmann et al., 2011; Yokoyama et al., 2014). A frequent problem related to unhealthy diet is a condition of overweight/obesity. The prevalence of obesity has increased rapidly worldwide over the past decades (NCD Risk Factor Collaboration, 2016). The Nurses' Health Study suggests that obesity is responsible for about 40% of hypertension, whereas the Framingham Offspring Study suggested that obesity is responsible for a higher prevalence of hypertension, with differences between males and females (Forman et al., 2009; Garrison et al., 1987). Lelong and colleagues (2019) reported that healthy weight represents a significant strong protective factor for hypertension in a large cohort of European adults. Accordingly, in a cross-sectional study conducted by Shen and collaborators (2017), a condition of overweight/obesity was found to be a risk factor for hypertension. Additional studies demonstrated that factors related to overweight/obesity, such as general adiposity (Andriolo et al., 2019), waist circumference (Meng et al., 2011) and high BMI (Nguyen et al., 2019), increase the risk of reporting high blood pressure values.

The global prevalence of alcohol consumption varies considerably, with lower rates in North Africa and Middle East and higher rates in Central and Eastern Europe (Mills et al., 2020). Numerous studies reported that alcohol consumption is a relevant risk factor for the onset and a worse prognosis of hypertension (Fuchs et al., 2001; Klatsky et al., 1977; Nguyen et al., 2019; Shen et al., 2017). Fuchs et al. (2001) suggested that high levels of consumption of all types of alcoholic beverages were associated with a higher risk of hypertension for several ethnic groups, whereas in a meta-analysis conducted by Xin and colleagues (2001) a reduction in alcohol intake was found to be associated with decreased values in both systolic and diastolic blood pressure.

Regarding physical activity, rates of insufficient physical exercise (defined as less than 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity physical activity per week, or any equivalent combination of these) seem to be quite high, with differences related to gender, ethnicity and countries (Guthold et al., 2018). Low physical activity levels seem to increase the risk of essential hypertension (Andriolo et al., 2019; Nguyen et al., 2019; Pantell et al., 2019). Furthermore, as reported by randomized controlled trials and meta-analyses (Ishikawa et al., 1999;

Kelley & Kelley, 2000; Whelton et al., 2002), adequate physical activity, particularly aerobic exercise, reduces BP in both hypertensive patients and normotensive individuals.

Finally, according to literature, cigarette smoking has been found to be associated to blood pressure levels increase, especially through the stimulation of the sympathetic nervous system (Baer & Radichevich, 1985; Rhee et al., 2007; Virdis et al., 2010). Several recent studies (Andriolo et al., 2019; Nguyen et al., 2019; Pantell et al., 2019; Song et al., 2020) demonstrated that smoking plays a relevant role in increasing the risk of hypertension development. Nevertheless, the long-term effects on blood pressure values and hypertension appear to be inconclusive (Bowman et al., 2007; Halperin et al., 2008; Virdis et al., 2010), making difficult to assume a direct causal association between smoking and essential hypertension.

### 1.4.4 Psychosocial factors

As demonstrated by several studies (Cuevas et al., 2017; Yan et al., 2003), psychosocial factors may have a role in the risk of hypertension onset and progression. Both psychological and social factors may act as contributors to the development of essential hypertension, promoting physiological responses as well as the activation of the sympathetic nervous system and the HPA axis (Black & Garbutt, 2002; Spruill, 2010).

Affective symptomatology often co-morbid with chronic medical diseases such as essential hypertension. Particularly, both depression and anxiety were found to be associated to an increased risk of hypertension (Allgulander, 2016; Cuevas et al., 2017; Jonas & Lando, 2000; Meng et al., 2012). As to depression, it seems to contribute to cardiac mortality and morbidity (Carney et al., 2002), and its association with hypertension has been widely recognized. Meng and colleagues (2012) conducted a meta-analysis of prospective studies demonstrating that depressive symptomatology represents an independent risk factor for hypertension, predicting more than 40% increased risk of hypertension incidence. In a prospective longitudinal study, Jackson and collaborators (2016) found that, among middle-aged women, depression was associated to a 30%

increased hypertension, even though lifestyle and socio-economic factors may have confounded this association. Regarding anxiety, it has been considered as a relevant driver of somatic morbidity favoring mortality rates (Allgulander, 2016). Anxiety symptomatology emerged as one of the most important risk factors for cardiovascular diseases (Allgulander, 2016; Frasure-Smith & Lespérance, 2008; Roest et al., 2010). Similarly to findings reporting on depression, a meta-analysis of prospective studies (Pan et al., 2015) demonstrated that anxiety symptomatology represents an independent risk factors for incident hypertension. In a population-based study conducted by Wu and colleagues (2014), Authors reported that patients with anxiety showed a higher prevalence of hypertension in comparison to the general population. Further, results showed that the average incidence of hypertension was higher in patients with anxiety disorders compared to general population, supporting the role of anxiety in the incidence of high blood pressure levels regardless of age and gender (Wu et al., 2014).

Yan et al. (2003) carried out a population-based prospective observational study using data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Results displayed that higher levels of two main components of Type A behavior, time urgency/impatience and hostility, were significantly associated to the risk of developing hypertension at 15-years follow-up (Yan et al., 2003).

Regarding the role of psychosocial stress in arterial hypertension, a systematic review and meta-analysis was conducted by Liu and colleagues (2017). Results showed that hypertensive patients reported a higher incidence of psychosocial stress compared to normotensive controls and that chronic psychosocial stress was associated to a greater risk of hypertension. A cross-sectional study carried out by Lu and colleagues (2019) considering a sample of Asian Americans, highlighted the relevance of perceived stress in understanding the clinical course of hypertension. Authors reported that individuals with high levels of perceived stress were more likely to report hypertension in comparison to those with low levels of perceived stress (Lu et al., 2019). Allostatic load (AL), defined as the cumulative effect of experiences in daily life involving ordinary events as well as major challenges (i.e., life events) (McEwen, 1998a, 2007; McEwen & Stellar, 1993), was linked to increased risk for cardiovascular diseases, including coronary heart disease (Gillespie et al., 2019), ischemic heart disease (Sabbah et al., 2008) and peripheral arterial disease (Nelson et al., 2007). Borrell and colleagues (2020) reported that higher levels of allostatic load were associated with higher all-cause and CVD-specific mortality rates among U.S. adults aged 25 years or older.

Social relationships may act as sources of emotional, informational and instrumental support reducing negative effects of stressful experiences and enhancing the individual ability to cope (Cuevas et al., 2017). Social support is also supposed to affect hypertension risk (Cuffee et al., 2014; Spruill, 2010). For instance, a study using National Health Interview Survey data found that emotional support and social integration were independently associated with a decreased risk of hypertension (Gorman & Sivaganesan, 2007). Furthermore, Sneed and Cohen (2014), using data from the Health and Retirement Study, found that negative social interactions were associated with increased risk of hypertension among older adults.

Hypertension symptomatology and accompanying complications appear to significantly decrease patients' quality of life (Carvalho et al., 2013). However, several studies on the association between hypertension and quality of life yielded mixed results (Li et al., 2018; Riley et al., 2019; Snarska et al., 2020). Regarding psychological well-being, it seems to have a protective role on cardiovascular system (Boehm & Kubzansky, 2012; Kubzansky et al., 2018; Trudel-Fitzgerald et al., 2014). Trudel-Fitzgerald and colleagues (2014) conducted a prospective study on the association of psychological well-being and hypertension using data from the Whitehall II cohort. Authors found that emotional vitality was associated with reduced risk of hypertension (Trudel-Fitzgerald et al., 2014).

**Chapter 2**. Treatment adherence in essential hypertension

## 2.1 Treatments for essential hypertension

According to the most recent guidelines (Williams et al., 2018), the major treatment strategies to lower blood pressure levels include pharmacological treatment and lifestyle interventions. A further emerging strategy is represented by the device-based therapy, even though its effectiveness must be proven (Williams et al., 2018). Most hypertensive patients require pharmacological treatment, but additional lifestyle modifications may certainly lower blood pressure values as well as cardiovascular risk (Mancia et al., 2013; Piepoli et al., 2016; Williams et al., 2018). Particularly, several meta-analyses (Brunstrom & Carlberg, 2018; Ettehad et al., 2016; Thomopoulos et al., 2014) have reported that a reduction of 10mmHg in systolic blood pressure or 5mmHg in diastolic blood pressure is associated with a significant reduction in all-cause mortality and major cardiovascular events including stroke, coronary events and heart failure.

Further, treatments for essential hypertension have a role in the reduction of chronic kidney disease development. Blood pressure reduction appears to have a protective effect on kidney functions, even though this seems to be limited to patients with comorbid diabetes (Lv et al., 2013). All patients with grade 2 or 3 hypertension should receive both pharmacological treatment and lifestyle interventions (Kjeldsen et al., 2014; Williams et al., 2018).

As to patients with grade 1 hypertension, a number of meta-analyses (Brunstrom & Carlberg, 2018; Sundtrsom et al., 2015; Thomopoulos et al., 2014) have shown a significant treatment-induced reductions in both mortality and cardiovascular events. Findings from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial (Lonn et al., 2016) supported these data, showing a significant association between SBP and major cardiovascular events reduction due to hypertensive medications in patients with grade 1 hypertension at intermediate cardiovascular risk. Therefore, the most recent guidelines (Williams et al., 2018) recommend drug treatment accompanied by lifestyle advices in patients with grade 1 hypertension at low-moderate cardiovascular risk.

As previously recommended (Mancia et al., 2013), individuals with high-normal blood pressure levels and low/moderate cardiovascular risk should not be treated with antihypertensive medications. As reported in several RCTs and meta-analyses (Brunstrom & Carlberg, 2018; Lonn et al., 2016; Thomopoulos et al., 2014, 2017), in patients at low/moderate cardiovascular risk and with baseline blood pressure levels at normal range, BP-lowering pharmacological treatment has shown no effects on cardiovascular outcomes. Therefore, patients with high-normal blood pressure levels and low/moderate cardiovascular risk should follow lifestyle advices in order to reduce risk of cardiovascular issues.

Earlier treatments for patients with systolic or diastolic blood pressure values more than 140/90mmHg with a low-moderate cardiovascular risk may prevent HMOD and residual risk due to treatment failure (Williams et al., 2018). Thus, preventing the development of high cardiovascular risk with earlier intervention appear to be an effective strategy (Williams et al., 2018). The first aim of blood pressure lowering medications should be to lower blood pressure values to < 140/90mmHg in all patients. If the pharmacological treatment is well tolerated, BP values should be targeted to 130/80mmHg (Williams et al., 2018). However, systolic blood pressure levels should not be targeted to less than 120mmHg, since the risk of damage seems to increase outweighing the benefits (Bohm et al., 2017).

### 2.1.1 Antihypertensive medications

In order to achieve an optimal blood pressure control, most patients require pharmacological treatment in addition to lifestyle modifications. The five major drug classes recommended for the treatment of hypertension include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers and diuretics. Recent meta-analyses (Emdin et al., 2015; Ettehad et al., 2016; Thomopoulos et al., 2015a, 2017) supported the role of these pharmacological classes in reducing blood pressure, cardiovascular events risk, morbidity and mortality. However, for each class of medications there are compelling or possible contraindications as well as differences in persistence and discontinuation rates (Corrao et al., 2008; Thomopoulos et al., 2016).

### 2.1.1.1 ACE inhibitors

Angiotensin-converting enzyme inhibitors represent one of the most widely prescribed classes of antihypertensive medications with proven effectiveness on blood pressure control, major cardiovascular events and mortality (Ettehad et al., 2016; Stapff & Hilderbrand, 2019; Thomopoulos et al., 2015a). Further, ACE inhibitors may reduce albuminuria and may delay the progression of both CKD (Thomopoulos et al., 2017) and HMOD (Thomopoulos et al., 2015a). Angiotensin-converting enzyme inhibitors may also reduce the incidence of atrial fibrillation (Thomopoulos et al., 2015a) and are particularly indicated for patients with complications due to hypertension, such as myocardial infarction and heart failure with reduced ejection fraction (Williams et al., 2018).

### 2.1.1.2 Angiotensin receptor blockers

Similarly to ACE inhibitors, angiotensin receptor blockers (ARBs) are one of the most used and effective classes of drugs prescribed to lower blood pressure levels (Ettehad et al., 2016; Williams et al., 2018). This class of antihypertensive medications is associated with significantly lower discontinuation rates due to side effects in comparison to all other antihypertensive therapies (Kronish et al., 2011). ARBs and ACE inhibitors should not be combined due to the lack of added benefits on cardiovascular outcomes and to increased risk of renal adverse events (Fried et al., 2013; ONTARGET investigators, 2008). Angiotensin receptor blockers are also effective in reducing albuminuria, CKD (Thomopoulos et al., 2017), HMOD and atrial fibrillation (Thomopoulos et al., 2015a). Further, this subgroup of renin-angiotensin system blockers should be preferred for individuals of Black African origins since angiotensin-converting enzyme inhibitors may be associated with a small increased risk of angioneurotic oedema in this specific population (Williams et al., 2018).

#### 2.1.1.3 Beta-blockers

As reported by several RCTs and meta-analyses (Thomopoulos et al., 2015b), beta-blockers have been shown to be significantly effective in reducing the risk of stroke, heart failure and other major cardiovascular events in patients with hypertension. This type of antihypertensive medications seems to be particularly useful in treating hypertension in particular circumstances, such as symptomatic angina, postmyocardial infarction and heart failure with reduced ejection fraction (Williams et al., 2018).

However, beta-blockers have shown a less favorable adverse events profile as well as higher discontinuation rates when compared to both ACE inhibitors and ARBs (Corrao et al., 2008). Further, individuals with metabolic syndrome should avoid this pharmacological class due to its association with increased risk of new-onset diabetes (Williams et al., 2018). Classical beta-blockers appear to be less effective than renin-angiotensin system blockers as to left ventricular hypertrophy, carotid intima–media thickness and aortic stiffness prevention (Mancia et al., 2013); however, vasodilating beta-blockers, such as nebivolol, seem to have no side effects in relation to diabetes and sexual function with more favorable effects on aortic stiffness and other cardiovascular events (Ayers et al., 2012; Bakris et al., 2004).

#### 2.1.1.4 Calcium channels blockers

Calcium channels blockers are widely prescribed for treating hypertension. This heterogeneous class of agents have shown to be effective on blood pressure levels, major cardiovascular events and mortality rates (Ettehad et al., 2016; Thomopoulos et al., 2015a). Further, calcium channels blockers appear to have a great effect on stroke reduction, even though they may be less effective for the prevention of heart failure with reduced ejection fraction (Ettehad et al., 2016; Thomopoulos et al., 2015a). When compared to beta-blockers, calcium channels blockers have shown to be more effective in decreasing the progression of several clinical conditions, such as left ventricular hypertrophy, proteinuria and atherosclerosis (Mancia et al., 2013).

#### 2.1.1.5 Diuretics

Diuretics (i.e., thiazide and thiazide-like diuretics) represent a class of antihypertensive drugs with reported effectiveness in preventing cardiovascular morbidities and mortality (Thomopoulos et al., 2015b). Furthermore, diuretics seem to be more effective than other classes of medications for the prevention of heart failure (Thomopoulos et al., 2015a). Several RCTs (Olde Engberink et al., 2015; Roush et al., 2015; Thomopoulos et al., 2015b; Zanchetti & Mancia, 1997), compared the effectiveness rates of classical diuretics (i.e., hydrochlorothiazide) and thiazide-like diuretics (i.e., chlortalidone and indapamide). Findings showed that thiazide-like diuretics are associated with cardiovascular benefits and longer duration of action (Olde Engberink et al., 2015; Roush et al., 2015; Thomopoulos et al., 2015b; Zanchetti & Mancia, 1997).
Although the debate about the preference of thiazide-like diuretics over classical diuretics, there is no evidence from direct comparator trials demonstrating the superiority of thiazide-like diuretics on cardiovascular outcomes (Williams et al., 2018). Therefore, the most recent guidelines (Williams et al., 2018) recommend the use of both classical and thiazide-like diuretics.

#### 2.1.1.6 Other

Drugs used for treating high blood pressure when other treatments where not available, are definitely less frequently prescribed mainly due to poor tolerability (Williams et al., 2018). For instance, alpha-blockers have been shown to be effective in the Anglo-Scandinavian Cardiac Outcomes Trial (Chapman et al., 2008) as a third-line strategy. However, in another study (Williams et al., 2015) Authors reported that alpha-blockers were less effective of a specific diuretic drug (i.e., spironolactone) in reducing blood pressure in resistant hypertension. Alpha-blockers may be useful in specific situations, for instance for the treatment of symptomatic prostatic hypertrophy (Williams et al., 2018).

#### 2.1.1.7 Drug combinations

Despite the amount of RCTs about antihypertensive therapies, just few trials reported data on different two-drug combinations comparisons (Williams et al., 2018). In several studies treatment started with a monotherapy followed by the addition of another medication whereas in others multiple monotherapies were evaluated (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). According to literature, diuretics are the pharmacological class of antihypertensive most frequently combined with other antihypertensive drugs, although the studies often included older patients (Beckett et al., 2008; Coope & Warrender, 1986; Dahlof et al., 1991; Lithell et al., 2003; SHEP Cooperative Research Group, 1991). Findings from placebo-controlled studies assessing the efficacy of combined antihypertensive drugs used in at least one active arm show that combinations of diuretics with ACE (Beckett et al., 2008; Patel et al., 2007; Williams et al., 2008), angiotensin receptor blockers (Lithell et al., 2003), calcium channel blockers (Liu et al., 2005) and beta-blockers (Coope & Warrender, 1986; Dahlof et al., 1991; SHEP Cooperative Research Group, 1991) have been associated with significant reductions in cardiovascular events risk, particularly strokes. Similarly, the Systolic Hypertension in China (Wang et al., 2000) and the Systolic Hypertension in Europe (Staessen et al., 1997) research groups reported that older patients with isolated systolic hypertension treated with a combination of ACE inhibitors and calcium channel blockers showed significantly lower rates of cardiovascular events compared to controls. Trials comparing different regimens (i.e., antihypertensive drugs combinations in both active arms) reported no major differences in terms of cardiovascular benefits (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; Black et al., 2003; Hansson et al., 2000; Matsuzaki et al., 2011; Ogihara et al., 2015; Pepine et al., 2003; Zanchetti et al., 2007). However, in two studies (Dahlof et al., 2002; McKavanagh et al., 2015) conducted on hypertensive patients with left ventricular hypertrophy or related risk factors, both ARB-diuretic combination and calcium channel blockers-ACE inhibitors combination were superior to beta-blockers-diuretic combination in reducing the risk of cardiovascular events. In the ASCOT (Dahlof et al., 2005) and ACCOMPLISH (Jamerson et al., 2008) trials, the combination of ACE inhibitors and calcium channel blockers in hypertensive patients with risk factors was more effective in reducing cardiovascular events compared to both beta-blockers and ACE inhibitor combined with diuretics. Further, the study conducted by Dahlof and colleagues (2002) demonstrated that a diuretic combined with an ARB is more effective than a diuretic combined with a beta-blocker in reducing the risk of stroke. The most recent guidelines (Williams et al., 2018) confirm that all the five major antihypertensive medications classes could be combined with one another, with the exception of the ACE inhibitors and angiotensin receptor blockers concomitant use. More specifically, Williams and colleagues (2018) recommend that the pharmacological treatment of hypertension based on drugs combination should preferentially include combinations of ACE inhibitors or angiotensin receptor blockers with calcium channel blockers and/or diuretics. These combinations limit possible side effects and reduce the risk of both hypokalaemia and peripheral oedema (Williams et al., 2018).

The majority of hypertensive patients actually require combination therapy. Starting with combined antihypertensive medications appears to be more effective in lowering blood pressure levels than monotherapy, with low-dose combination therapy representing a better solution than maximal dose monotherapy (Wald et al., 2009). Further, initial treatment with two-drug combinations is associated with more frequent blood pressure control (Egan et al., 2012; Wald et al., 2009) and has been shown to be safe and well tolerated (Wald et al., 2009). These mechanisms may be due to better long-term adherence to prescribed treatment based on drug combinations (Corrao et al., 2010) as well as to reduced discontinuation rates and lower risk of cardiovascular events (Corrao et al., 2010, 2011). Even though approximately two-thirds of patients are able to control blood pressure values with two-drug combinations therapies (Wald et al., 2009), for those who remain the treatment option is a three-drug combination therapy with an ACE/ARB, calcium channels blocker or a diuretic (Volpe et al., 2012; Weir et al., 2011). Further, Lee and colleagues (2017) reported that a combination of an angiotensin receptor blocker, a calcium channels blocker and a statin may represent an effective therapeutic strategy in patients with both hypertension and dyslipidemia. When blood pressure could not be controlled with a three-drug combination therapy, the patient is classified as having resistant hypertension, excluding secondary causes of hypertension and poor adherence levels (Williams et al., 2018).

### 2.1.2 Lifestyle modifications

It is widely recognized that healthy lifestyle habits may prevent or delay the onset of hypertension, reducing blood pressure levels and cardiovascular risk (Mancia et al., 2013; Piepoli et al., 2016; Winnicki et al., 2006). Further, lifestyle modifications as nonpharmacological interventions for hypertensive patients allow to reduce antihypertensive medications dosage (Mahmood et al., 2019). As confirmed by the most recent guidelines for the management of arterial hypertension (Williams et al., 2018), adequate lifestyle changes may prevent the need for medications in patients with grade 1 hypertension. Effective lifestyle modifications may also increase the effects of blood pressure lowering treatments, even though they should never delay the initiation of pharmacological therapies in patients with HMOD or in patients at high cardiovascular risk (Williams et al., 2018). Recommended lifestyle habits that have been shown to be effective in lowering blood pressure levels include a healthy diet, moderated alcohol consumption, weight reduction, maintenance of adequate body weight and regular physical activity (Mancia et al., 2013; Williams et al., 2018). Furthermore, smoking cessation, sleep quality and stress management may have a role in preventing high levels of blood pressure (Blumenthal et al., 2002; Lo et al., 2018; Piepoli et al., 2016).

2.1.2.1 Diet

Adopting a healthy diet is an effective strategy in order to prevent the onset of hypertension in individuals with normal blood pressure values and to improve BP control in hypertensive patients (Appel et al., 2006; Chobanian et al., 2003). According to literature, sodium restriction as well as increased potassium intake and high consumption of fruit and vegetables have a relevant role in the management of essential hypertension (Blumenthal et al., 2002; He & Bazzano, 2000; Mahmood et al., 2019; Mancia et al., 2013; Samadian et al., 2016; Shimbo, 2016; Williams et al., 2018). Sodium intake seems to have a causal association with increased blood pressure values and a consumption of > 5g sodium per day tends to increase the prevalence of hypertension and BP levels over time (Elliot et al., 1996). Accordingly, many trials demonstrated that sodium restriction has been shown to have a blood pressure lowering effect (Cappuccio et al., 1997; He et al., 2013; Whelton et al., 1998). A meta-analysis conducted by He and collaborators (2013) revealed that a reduction of 1.75g sodium per day was associated with a reduction of 4.2/2.1mmHg in systolic/diastolic blood pressure, with a greater effect in patients with hypertension. Further, the effect of sodium reduction on BP levels appears to be more pronounced in Black individuals, older patients and patients with diabetes, metabolic syndrome or chronic kidney disease (Suckling et al., 2016). As to the risk of cardiovascular events the role of reduced sodium remains unclear (Bibbins-Domingo et al., 2010; He & MacGregor, 2011; He et al., 2011; Taylor et al., 2011). In a study published by He and colleagues (1999), findings showed a strong and independent associations between high sodium intake and both increased risk of cardiovascular events and all-cause mortality in overweight individuals. Further, some trials and meta-analyses suggest that a moderate consumption of salt in comparison to high is linked to a lower risk of cardiovascular events (Aburto et al., 2013; He & MacGregor, 2011; Taylor et al., 2011). However, several prospective trials reporting an association between high cardiovascular events risk and overall increased risk of mortality, also reported that reducing sodium intake below a certain level was paradoxically associated with increased risk of mortality (Mente et al., 2016).

Increased potassium intake seems to have a protective effect against hypertension and has been associated with blood pressure reduction (Kawano et al., 1998; O'Donnell et al., 2014; Sacks et al., 1998). Whelton et al. (1997) conducted a meta-analysis to evaluate the effects of potassium supplementation on BP levels. Results showed that increased potassium intake was associated with a significant reduction in both systolic and diastolic blood pressure values (Whelton et al., 1997). A regular and balanced consumption of vegetables, legumes, fruit, low-fat dairy products, fish and unsaturated fats with a low consumption of red meat should characterize dietary habits of hypertensive patients (Dickinson et al., 2006; Mente et al., 2009; Sofi et al., 2010). Numerous studies (Dickinson et al., 2006; Estruch et al., 2018; Mente et al., 2009; Sofi et al., 2010) have shown that following the Mediterranean diet – a diet including many of these nutrients – may reduce the risk of cardiovascular events and all-cause mortality. Further, the Mediterranean diet appears to significantly reduce ambulatory blood pressure, blood glucose and lipid levels (Domenech et al., 2014). The Dietary Approaches to Stop Hypertension (DASH) diet has a clear and recognized blood pressure lowering effect reducing both systolic and diastolic BP values (Gay et al., 2016; Ndanuko et al., 2016; Sacks et al., 2001; Saneei et al., 2014; Siervo et al., 2015). The DASH diet is rich in fruit, vegetables and low-fat dairy products and has been shown to be more effective than control diet or diet based only on fruit and vegetables consumption (Appel, 2017; Appel et al., 1997).

Regarding coffee consumption, a systematic review with meta-analysis of prospective cohort studies about long-term coffee consumption and risk of cardiovascular disease highlighted the acute pressor effect of caffeine (Ding et al., 2014). However, the association between caffeine and cardiovascular benefits was also suggested (Ding et al., 2014). Consumption of green or black tea may also have a role in blood pressure values lowering, as pointed out by two systematic reviews (Greyling et al., 2014; Li et al., 2015). Conversely, since consumption of sugar-sweetened soft drinks has been associated with overweight, metabolic diseases, diabetes and greater cardiovascular risk (Piepoli et al., 2016), in hypertensive patients these beverages are often discouraged (Piepoli et al., 2016; Williams et al., 2018).

2.1.2.2 Alcohol consumption

A number of epidemiological and cross-sectional studies have demonstrated the role of alcohol use and abuse as risk factors for hypertension in several countries (Potter & Beevers, 1984; Shen et al., 2017). As suggested by Loyke (2013), there are five different phases describing the effects of alcohol on blood pressure. In the first phase, alcohol consumption is associated with increased BP levels depending on the amount of alcohol intake. During the second phase, alcohol abstinence reduces systolic and diastolic BP, whereas in phase 3 toxic effects may arise. Later, in phase 4, the individual is at high risk of liver damage which may occur, along with liver disease, in phase 5. The positive linear association between alcohol consumption, blood pressure, hypertension prevalence and cardiovascular diseases risk is well established (Williams et al., 2018). A meta-analysis including more than 50 epidemiological studies suggested that reducing alcohol consumption may benefit cardiovascular health (Holmes et al., 2014). Studies on alcohol detoxification support these findings, reporting BP levels of more than 140/90mmHg in most of individuals admitted for detoxification and a subsequent blood pressure reduction in 70% of them after detoxification (Potter & Beevers, 1984). Mechanisms through which alcohol increase BP seem to be related not to long-term structural alterations but to neural or further physiological changes (Samadian et al., 2016).

As recommended, men with hypertension should limit alcohol consumption to 14 units per week, whereas hypertensive women to 8 units per week, with 1 unit equal to 125ml of wine or 250ml of beer (Williams et al., 2018). Further, binge drinking should be avoided given its strong effect on blood pressure levels (Mancia et al., 2013; Piepoli et al., 2016).

2.1.2.3 Physical activity

Physical exercise indices increased levels of blood pressure, particularly systolic blood pressure, followed by short BP values decline. Engaging in regular physical activity, especially aerobic exercises, may have a protective effect on blood pressure and may lower cardiovascular events and mortality (Diaz & Shimbo, 2013; Williams et al., 2018; You et al., 2018). In addition, physical exercise has strong beneficial effects on further parameters including plasma components, particularly in hypertensive patients (Parto et al., 2015). A meta-analysis of RCTs reported that aerobic endurance training as well as dynamic resistance training and isometric training reduce both systolic and diastolic blood pressure in general population, with endurance training having a role also in hypertensive patients (Cornelissen & Smart, 2013). Cohort studies (Leitzmann et al., 2007; Rossi et al., 2012) reported that physical activity with low intensity and duration decreases blood pressure less than moderate- or high-intensity training, even though appears to be associated with 15% decrease mortality rates. As reported by a meta-analysis of RCTs (Börjesson et al., 2016), regular medium-to-high-intensity aerobic exercises lower blood pressure values by a mean of 11/5mmHg with isometric physical activity showing similar results. Therefore, this evidence highlights the need to engage at least 30 minutes of moderate-intensity dynamic aerobic exercises on 5-7 days per week as well as resistance exercises on 2-4 days per week in order to reduce or treat hypertension (Sharman et al., 2015; Williams et al., 2018).

The importance of adequate physical activity, especially for hypertensive patients, lies also in its effects on body weight. Excessive weight gain has been associated with high blood pressure values whereas its reduction to an optimal BMI tends to decrease both systolic and diastolic pressure (Hall et al., 2015; Neter et al., 2003). Overweight and obesity, which represent major problems in developed and developing countries (Chobanian et al., 2003), have been linked to increased risk of both cardiovascular events and mortality (Williams et al., 2018). Therefore, weight loss is recommended in overweight/obese patients with essential hypertension. Prospective Studies Collaboration (2009) have reported that mortality rates were lowest for individuals with a BMI of about 22.5/25 kg/m$^2$. Maintenance of a healthy body mass index as well as appropriate waist circumference is also recommended for preventing and reducing hypertension (Piepoli et al., 2016). Further, weight loss may improve antihypertensive medications efficacy and cardiovascular health (Williams et al., 2018). An optimal body weight should be achieved through a multidisciplinary approach including not only physical activity but also dietary advices and counselling (Jebb et al., 2011; Piepoli et al., 2016) or, alternatively, to a greater degree, trough anti-obesity drugs and bariatric surgery (Williams et al., 2018).

#### 2.1.2.4 Smoking habits

Smoking represents a major risk factor for several pathologies, including cardiovascular diseases and cancer. The prevalence of smoking rates in Europe is around 20-35%, even though it seems to decline in most countries (Kotseva et al., 2016). Further, passive smoking has been shown to have an ill-health effect (Akpa et al., 2021; Lee et al., 2017; Yarlioglues et al., 2010). Several studies have reported that both normotensive individuals and untreated hypertensive smokers show greater daily blood pressure levels compared to non-smokers (Groppelli et al., 1992; Saladini et al., 2016). However, no long-term effects were detected for office blood pressure, which tends to not decrease by smoking cessation (Primatesta et al., 2001). Thus, the most recent guidelines (Williams et al., 2018) recommend smoking cessation as the most effective lifestyle measure for preventing cardiovascular diseases, such as stroke, myocardial infarction and peripheral artery disease (Lim et al., 2012). History of tobacco use should be evaluated at each patient visit and hypertensive smokers should be advised to interrupt smoking habits (Williams et al., 2018). Physicians' advices may be improved by pharmacological measures, including varenicline or similar nicotine replacement therapies (Cahill et al., 2013), as well as behavioral support (Stead et al., 2016).

#### 2.1.2.5 Sleep quality

Elevated blood pressure levels and low sleep quality due to sleep problems and/or disorders often coexist. Low levels of sleep quality may represent a risk factor for the onset of essential hypertension (Gangwisch et al., 2006; Lo et al., 2017). Palagini and colleagues (2013) reported that experimental sleep deprivation, short sleep duration and persistent insomnia are all associated with increased blood pressure and increase risk of hypertension. The pathophysiological mechanisms underlying these associations may be linked to increased activation of stress system functions (Palagini et al., 2013). Thus, long-term sleep loss or impaired sleep quality may act as neurobiological stressors contributing to somatic diseases (Palagini et al., 2013). A recent meta-analysis (Han et al., 2020) confirmed these data showing that increased blood pressure was associated with obstructive sleep apnea, short and too long sleep duration, with snoring as a risk factor for hypertension. Therefore, keeping a good sleep hygiene may contribute to improve cardiovascular health.

#### 2.1.2.6 Stress management

According to literature, physiological stress is positively associated with elevated blood pressure values and essential hypertension (Blumenthal et al., 2002; Sparrenberger et al., 2009). Further, some evidence (Guidi et al., 2020) report that allostatic overload – a condition that may ensue when environmental challenges exceed the individual ability to cope (Fava et al., 2019; McEwen & Wingfield, 2003) – has been shown to be present in patients with essential hypertension. Thus, stress management strategies with the aim to reduce excessive stress arousal eliciting a relaxation physiological response may be useful. For instance, yoga, combining both breathing and meditation techniques, appears to exert a positive effect in patients with arterial hypertension (Cramer, 2016; Cramer et al., 2018; Tyagi & Cohen, 2014). Furthermore, it seems that also meditation techniques may have a role in decreasing blood pressure levels, particularly in older patients (Park & Han, 2017).

## 2.2 Associations between psychosocial factors and treatment adherence

Since high blood pressure management requires both long-term pharmacological and non-pharmacological therapies, adherence to prescribed treatment appears to be certainly crucial (Brown & Bussell, 2011; Nakao et al., 2003; Williams et al., 2018) but approximately 50-70% of patients do not follow prescribed treatments (Mant & McManus, 2006). Despite the fact that non-adherence to pharmacological treatment may cause hypertension-related morbidity and mortality as well as unnecessary overprescriptions and disease worsening (Mazzaglia et al., 2009; Ogden et al., 2000), the rate of adherence to anti-hypertensive medications is roughly as high as 50% (WHO, 2003). The role of adherence as to both pharmacological and non-pharmacological antihypertensive treatments is well recognized. Treatment early discontinuation and a suboptimal use of prescribed therapies represent the most common aspects of poor adherence (Williams et al., 2018). Regarding antihypertensive medications, studies considering urine or blood assays have reported low rates of treatment adherence among patients (Williams et al., 2018). Further, several trials on general population have shown that adherence to treatment based on prescription refilling was less than 50% in the half of patients (Corrao et al., 2011). Previous (Mancia et al., 2013) and current (Williams et al., 2018) guidelines suggested the use of combination of two antihypertensive medications in a single pill, since reducing the number of pills to be taken daily seems to increase adherence rates (Corrao et al., 2010; Gupta et al., 2010). Furthermore, persistence of lifestyle modifications, especially dietary habits and physical activity, tend to decrease over time (Williams et al., 2018).

Low adherence levels were associated with both poor blood pressure control (Corrao et al., 2008; Mazzaglia et al., 2009; Schutte et al., 2015) and increased risk of cardiovascular events (Tiffe et al., 2017; Welsh et al., 2019). The multifactorial nature of poor adherence to antihypertensive treatments is recognized. Boundaries to optimal adherence rates have been associated with physicians' attitudes, patients' beliefs and behaviors, complexity and tolerability of pharmacological treatment as well as other clinical and psychosocial factors (Krousel-Wood et al., 2004, 2009; Williams et al., 2018).

### 2.2.1 Psychological distress

Psychological distress represents one of the recognized factors affecting treatment adherence, especially in the clinical field of cardiovascular diseases. As reported by a recent cross-sectional study (Doubova et al., 2017) hypertension-related distress has been associated with poor adherence to prescribed treatment, especially with physical activity and dietary recommendations. Authors, considering a sample of hypertensive adults, have found that more than 20% reported hypertension-related distress, whereas low adherence to both pharmacological treatment and lifestyle recommendations were observed in more than 45% of the sample (Doubova et al., 2017). Depressive symptomatology appears to be frequent in patients with chronic illnesses, including arterial hypertension, and has been associated with adverse health outcomes and hypertension complications (Scalco et al., 2005). Further, high depression levels seem to be significantly negatively correlated to medication adherence in hypertensive patients (Burnier et al., 2020; Demirtürk, & Hacıhasanoğlu Aşılar, 2018). As to anxiety, longitudinal and cross-sectional trials (Johnson, 2019) have reported a positive association between prevalent or incident essential hypertension and comorbid anxiety. Further, anxiety symptoms seem to be a relevant risk factor for cardiovascular diseases (Allgulander, 2016; Frasure-Smith & Lespérance, 2008; Roest et al., 2010) and incident hypertension (Pan et al., 2015). In a longitudinal cohort study, Bautista and colleagues (2012) have been shown that hypertensive patients with comorbid anxiety taking antihypertensive medications were more likely to become nonadherent over time, suggesting the role of affective symptomatology in treatment adherence prevalence. Similarly, hostility and irritability seem to increase the risk of reporting hypertension over time (Yan et al., 2003). Hostility levels have shown to be higher in individuals skipping medications dosage in comparison to those complied with the prescribed drugs schedule (Lee et al., 1992).

### 2.2.2 Abnormal illness behavior

Illness behavior was defined by Mechanic and Volkart (1960) as “the ways in which given symptoms may be differentially perceived, evaluated, and acted (or not acted) upon by different kinds of persons”. Later, Mechanic (1995) specified that illness behavior represents not only the different ways patients respond to body indications, but also how they monitor, define and interpret symptoms and take actions through several sources. The clinical spectrum of illness behavior includes several psychosomatic syndromes, such as hypochondriasis, disease phobia, thanatophobia, health anxiety, persistent somatization, conversion symptoms, anniversary reaction and illness denial (Fava et al., 2017). Illness behavior may be associated with elevated blood pressure levels. In a study conducted by Guidi and colleagues (2020) among patients with essential hypertension almost 30% reported illness denial, the tendency to do not admit the presence or severity of the illness (Fava et al., 2017).

### 2.2.3 Allostatic load/overload

McEwen & Stellar (1993) introduced the concept of allostatic load referring to the cost of chronic exposure to variable and enhanced neural and neuroendocrine responses due to repeated or chronic stressful environmental challenges. The allostatic load represents the cumulative effect of daily life experiences involving ordinary events as well as life events (McEwen, 1998a, 2007; McEwen & Stellar, 1993). Further, this concept also includes the physiological consequences due to health damaging behaviors. Allostatic overload may ensue when environmental challenges exceed the individual ability to cope (Fava et al., 2019; Guidi et al., 2021; McEwen & Wingfield, 2003). Several situations may contribute to the development of both allostatic load and overload, including the exposure to frequent stressors determining a repeated physiological arousal, the lack of adaptation to repeated stressors, the inability to shut off the subsequent responses after a stressor is terminated and the inability to deal with the stressors because of not sufficient allostatic responses (McEwen, 1998b, 2008). Allostatic load and overload activate several physiological systems including neuroendocrine and immune systems (McEwen, 1998b, 2007) as well as the HPA axis (Chrousos, 2009; McEwen, 2007). Furthermore, these conditions contribute to a number of alterations in cardiovascular and gastrointestinal systems, endocrine-metabolic balances and sleep quality (Agorastos et al., 2019; Chrousos, 2009; McEwen, 2007, 2015). Allostatic load and overload seem to be particularly related to cardiovascular health (Borrell et al., 2020; Gillespie et al., 2019; Gostoli et al., 2016; Guidi et al., 2016, 2020; Nelson et al., 2007; Offidani et al., 2013; Porcelli et al., 2012; Sabbah et al., 2008). As previously reported, several studies have shown that allostatic load was associated to increased risk for cardiovascular diseases (Gillespie et al., 2019; Nelson et al., 2007; Sabbah et al., 2008). In a study conducted on outpatients with essential hypertension and coronary heart disease (Porcelli et al., 2012), allostatic overload was associated with disease-related emotional burden, poor psychosocial functioning and high psychopathology rates. In another study (Guidi et al., 2020), hypertensive patients with allostatic overload displayed significantly higher levels of psychological distress and a greater prevalence of psychosomatic syndromes, compared to those without.

### 2.2.4 Psychological reactance

Psychological reactance was defined as a motivational state that may ensue when individual freedom is threatened, in order to restore the perception of autonomy (Brehm, 1966, 1972; Brehm & Brehm, 1981). Several studies conducted by De las Cuevas and colleagues (2014a, 2017, 2021), have shown that, in psychiatric patients, adherence to prescribed pharmacological treatments was negatively associated with psychological reactance. As to hypertension, Abel and Barksdale (2012), suggested that psychological reactance may contribute to poor adherence levels in hypertensive patients.

2.2.5 Psychological well-being and quality of life

According to literature, psychological well-being seems to be associated with a better cardiovascular health (Boehm & Kubzansky, 2012; Kubzansky et al., 2018¸ Trudel-Fitzgerald et al., 2014). Psychological well-being tends to consistently protect against several cardiovascular diseases (Boehm & Kubzansky, 2012) and has been shown to be negatively associated with high blood pressure levels (Hildingh & Baigi, 2010; Trudel-Fitzgerald et al., 2014). As to quality of life, hypertensive patients tend to report low levels of health-related quality of life compared to those without (Riley et al., 2019; Ye et al., 2018) or to those with further comorbidities (Soni et al., 2010). High levels of quality of life among hypertensive patients have been found to be positively associated with adherence to both pharmacological and non-pharmacological prescribed treatments (de Souza et al., 2016; Jneid et al., 2018; Khayyat et al., 2019; Park et al., 2018). A systematic review with meta-analysis conducted by de Souza and colleagues (2016) reported an average significant increase in quality of life levels in hypertensive patients adhering to both pharmacological treatment and lifestyle recommendations.

# Chapter 3. Experimental studies

## 3.1 Aims and hypotheses

### 3.1.1 *Cross-sectional study*

Previous research findings (Abel & Barksdale, 2012; Bautista et al., 2012; Burnier et al., 2020; de Souza et al., 2016; Doubova et al., 2017; Guidi et al., 2020; Mocayar-Maron et al., 2019; Porcelli et al., 2012; Riley et al., 2019; Trudel-Fitzgerald et al., 2014) have shown that hypertension longitudinal course and prognosis as well as treatment adherence may be influenced by certain psychosocial factors.

A cross-sectional study was conducted with the purpose to assess the predictive role of a comprehensive assessment of psychosocial factors (i.e., psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, psychological well-being and quality of life) on adherence to antihypertensive medications, lifestyle behaviors, hypertension severity and absolute cardiovascular risk grading in a sample of hypertensive patients. Further, we expected to identify subgroups of hypertensive patients characterized by specific psychological profiles.

### 3.1.2 *Longitudinal study*

A longitudinal study was carried out in order to evaluate the temporal stability as well as possible variations over time of psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, well-being and quality of life, at one-year follow-up.

### 3.1.3 *Validation study*

Since the construct of psychological reactance (Brehm, 1966, 1972; Brehm & Brehm, 1981) was found to be associated with both hypertension clinical course and adherence to pharmacological treatment (Abel & Barksdale, 2012; De las Cuevas et al., 2014a, 2017), a validation study was carried out in order to validate the Italian version of the most studied measure of trait reactance: the Hong Psychological Reactance Scale (Hong & Page, 1989). According to literature, we expected to find a satisfactory internal consistency reliability and factorial structure of the Italian adaptation of the Hong Psychological Reactance Scale, taking into account previous findings on the original English version of the instrument (Hong, 1992; Hong & Page, 1989; Jonason, 2007; Jonason & Knowles, 2006).

### 3.2 Participants and procedures

#### 3.2.1 *Cross-sectional study*

Eighty patients (G*Power version 3.1.9.4, Germany) (42 men, 52.5%; 38 women, 47.5%; mean age 55.23 ± 9.48 years; age range 22-69 years) affected by essential hypertension were consecutively recruited from the Arterial Hypertension Clinic of Internal Medicine Division at the Bufalini Hospital in Cesena (Italy). All patients were taking antihypertensive medications (i.e., angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, β-blocking agents, diuretics, statins and drugs combinations).

Participants were included if they have received a diagnosis of essential hypertension by their cardiologist or general practitioner, were adults (18-70 years old) and had a current prescription of at least one antihypertensive medication.

Participants were excluded if they were

- $< 18$ or $\geq 70$ years old;
- Unable to speak Italian;
- Recognized as having cognitive impairments;
- Unable to provide the informed consent form voluntarily or denied it.

Furthermore, eighty normotensive control subjects, matched for age and gender (35 men, 43.7%; 45 women, 56.2%; mean age 51.78 ± 10.53; age range 24-69 years), were recruited from general population.

Sociodemographic and clinical characteristics of both hypertensive patients and normotensive controls are reported in **Table 1**. Data on cardiac variables were collected from medical records. Further medical variables considered included current medical or psychiatric illnesses, past hospitalizations and surgeries, allergies and current medications. The most frequently reported medical comorbidities were cancer and diabetes.

Cardiologist and nurses screened eligible hypertensive patients attending the clinic during the entire enrollment period. Written informed consent and personal information treatment consent were obtained from all participants, after the procedures were fully explained. The study was approved by the institutional review boards.

### 3.2.2 *Longitudinal study*

Thirty-eight patients (47.5% of total sample; 19 men, 50%; 19 women, 50%; mean age 55.42 ± 9.05 years; age range 33-69 years) have been reassessed after one-year follow-up so far. They were all on antihypertensive medications (i.e., angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, β-blocking agents, statin and drugs combinations). Written informed consent and personal information treatment consent were reobtained from all participants and longitudinal evaluations were also approved by the institutional review boards.

### 3.2.3 *Validation study*

The Italian version of the Hong Psychological Reactance Scale was administered to 30 Italian volunteer subjects, recruited from general population, to test intelligibility of the translated items (Perneger et al., 2015).

Further, one hundred and fifty individuals from general population recruited in the Northern and Central Italy between December 2018 and March 2019 provided data for the validation study. The mean age of the sample was 51.6 (SD: 13.04), ranging from 18 to 75 years. Participants were mostly female (54.7%) and almost 50% reported a high educational status.

**Table 1.** Sociodemographic and clinical characteristics of hypertensive patients and controls at baseline

| *Sociodemographic and clinical variables* | Hypertensive patients (n=80) | Normotensive individuals (n=80) | | |
|---|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *t* | *p* |
| Age (years) | 55.23 (9.48) | 51.78 (10.93) | 2.131 | .222 |
| | *n (%)* | *n (%)* | *χ2* | *p* |
| Gender | | | 1.227 | .268 |
| Male | 42 (52.5) | 35 (43.7) | | |
| Female | 38 (47.5) | 45 (56.2) | | |
| Educational status | | | 12.883 | **.005*** |
| Primary school | 2 (2.5) | 4 (5) | | |
| Secondary school | 29 (36.2) | 20 (25) | | |
| High school | 45 (56.2) | 37 (46.2) | | |
| Degree or more | 4 (5) | 19 (23.7) | | |
| Marital status | | | 3.089 | .543 |
| Not married | 16 (20) | 21 (26.2) | | |
| Married | 57 (71.2) | 49 (61.2) | | |
| Divorced/Separated | 6 (7.5) | 7 (8.7) | | |

| | | | | |
|---|---|---|---|---|
| Widowed | 1 (1.2) | 3 (3.7) | | |
| Occupational status | | | .027 | .869 |
| Employed | 51 (63.7) | 52 (65) | | |
| Retired/Unemployed | 29 (36.2) | 28 (35) | | |
| Physical comorbidities | 22 (27.5) | 16 (20) | 1.242 | 2.65 |
| Psychiatric comorbidities | 15 (18.7) | 11 (13.7) | .735 | .391 |
| Current medications | 80 (100) | 32 (40) | 63.823 | < **.001*** |
| Current psychotropic medications | 18 (22.5) | 15 (18.7) | .344 | .558 |
| Past hospitalization | 57 (71.2) | 40 (50) | 7.567 | **.006*** |
| Allergies | 14 (17.5) | 9 (11.2) | 1.296 | .260 |
| Smoking | 18 (22.5) | 28 (35) | 3.051 | .081 |
| Alcohol consumption | 5 (6.2) | 23 (28.7) | 14.026 | **< .001*** |
| Substance use | 0 (0) | 0 (0) | | |
| Adherence level | | | | |
| High | 46 (57.5) | | | |
| Good | 6 (7.5) | | | |
| Moderate | 9 (11.2) | | | |
| Poor | 16 (20) | | | |
| Very poor | 3 (3.7) | | | |
| Discontinuation | 0 (0) | | | |
| Hypertension grading | | | | |
| High normal | 6 (7.5) | | | |
| Grade 1 | 50 (62.5) | | | |
| Grade 2 | 7 (8.7) | | | |
| Grade 3 | 1 (1.2) | | | |

| | | |
|---|---|---|
| Isolated systolic hypertension | 4 (5) | |
| Absolute cardiovascular risk | | |
| Low | 28 (35) | |
| Moderate | 20 (25) | |
| High | 13 (16.2) | |
| Very high | 3 (3.7) | |
| Weight status | | |
| Normal weight | 29 (36.2) | |
| Overweight | 26 (32.5) | |
| Obesity | 14 (17.5) | |
| Abdominal obesity | 7 (8.7) | |
| Family history of CVD | 13 (16.2) | |
| | *Mean (SD)* | *Range (min-max)* |
| Resting heart rate (BPM) | 75.36 (11.71) | 54-98 |
| Systolic (mmHg) | 139.02 (12.9) | 110-170 |
| Diastolic (mmHg) | 83.05 (8.30) | 65-100 |
| | *n (%)* | |
| Duration of illness | | |
| 12 months or more | 64 (80) | |
| Less than 12 months | 14 (17.5) | |
| Organ damage | 20 (25) | |
| History of CVD | 7 (8.7) | |
| Diabetes | | |
| Type 1 | 1 (1.2) | |
| Type 2 | 3 (3.7) | |

| | | |
|---|---|---|
| Hyperglycemia | 5 (6.2) | |
| Hypercholesterolemia | 10 (12.5) | |
| Hypertriglyceridemia | 4 (5) | |
| | *Mean (SD)* | *Range (min-max)* |
| Glycaemia | 102.09 (23.9) | 73-199 |
| Creatinine | .89 (.18) | .63-1.33 |
| Total cholesterol | 195.27 (33.30) | 139-315 |
| HDL cholesterol | 60.3 (24.4) | 28-155 |
| LDL cholesterol | 115.87 (31.9) | 55-223 |
| Triglycerides | 132.5 (76.4) | 42-443 |

**p value < .05; CVD: cardiovascular diseases; HDL: high-density lipoprotein; LDL: low-density lipoprotein*

### 3.3 Assessment

#### 3.3.1 *Cross-sectional and Longitudinal studies*

For each study, data were collected administering clinical interviews and self-rating questionnaires at baseline and at one-year follow-up. Data were collected in person at the Arterial Hypertension Clinic or by phone when needed.

##### 3.3.1.1 The Clinical Interview for Depression

The Clinical Interview for Depression (CID; Guidi et al., 2011; Paykel, 1985) is an observer-rated tool, which has been derived from the Hamilton Rating Scale for Depression (Hamilton, 1967), for assessing a wide range of affective symptoms. The Clinical Interview for Depression covers a broad spectrum of symptom areas, with questions rated on 7-point scales, and three final scales (depression, anxiety and total scales) that could be obtained from patients' scores.

Each anchor point has specification based on severity, frequency and/or quality of symptoms. The instrument is set out as a semi-structured interview with items to be asked and rated in a specified order. Further, initial questions for each item may be modified if needed (Guidi et al., 2011). The Clinical Interview for Depression has been shown to be a valid and reliable instrument in order to rate depressive symptoms comprehensively and appears to be suitable for evaluating affective disorder symptomatology, due to its ability to measure small changes near the normal end of the spectrum (Guidi et al., 2011). Thus, the Clinical Interview for Depression tends to discriminate sensitively between acute or partially remitted patients with affective disorders and healthy subjects as well as different subgroups of patients across several treatment setting and has been extensively used in the medically ill (Guidi et al., 2011).

For the aims of both cross-sectional and longitudinal studies, the short version of the Clinical Interview of Depression (CID-20) was administered. The 20-item CID has been used extensively in clinical trials for repeated assessments and was found to be highly sensitive to clinical changes (Guidi et al., 2011).

#### 3.3.1.2 The Italian version of the semi-structured interview for the Diagnostic Criteria for Psychosomatic Research revised

The Italian version of the semi-structured interview based on the Diagnostic Criteria for Psychosomatic Research revised (DCPR-R-SSI; Fava et al., 2017) is a clinical interview for the assessment of 14 psychosomatic syndromes including:

- Allostatic overload
- Abnormal illness behavior (i.e., hypochondriasis, disease phobia, thanatophobia, health anxiety, illness denial)
- Somatization syndromes (i.e., persistent somatization, functional somatic symptoms secondary to a psychiatric disorder, conversion symptoms, anniversary reactions)

- Irritability
- Demoralization (with and without hopelessness)
- Personality characteristics (i.e., Type A behavior and alexithymia)

As previously described, allostatic overload may ensue when environmental challenges exceed the individual ability to cope (Fava et al., 2019; McEwen & Wingfield, 2003), leading to physiological dysregulations and favoring several illnesses. Fava and colleagues (2017) defined two diagnostic criteria for the diagnosis of allostatic overload. The first indicates the presence of a current identifiable source of distress as a recent life event and/or chronic stressor which exceeds the individual ability to cope. The second criterion associates the stressor to symptoms, significant impairment in social or occupational functioning or significant impairment in environmental mastery (Fava et al., 2017).

The clinical spectrum of illness behavior includes several psychosomatic syndromes. Hypochondriasis refers to the fears of having a serious disease based on misinterpretation of bodily symptoms. Disease phobia represents the persistent and unfounded fear, experienced trough attacks, of suffering from a specific illness despite adequate medical exams and reassurance. Thanatophobia is characterized by at least two attacks in the past 6 months of impending death and/or conviction of dying soon, without a real threatening situation or danger. Further, in thanatophobia there are marked and persistent fear and avoidance of stimuli related to death. The spectrum of illness behavior includes also health anxiety (the presence of worries and attitudes concerning illness and pain, less specific than in hypochondriasis and disease phobia, responding to medical reassurance) and illness denial (the lack of acknowledge about the presence or severity of the illness). As to somatization syndromes, persistent somatization refers to the presence of functional medical symptoms for more than six months causing distress as well as symptoms of autonomic arousal indicating enhanced general sensitivity to pain and discomfort. Patients may also experience functional somatic symptoms secondary to a psychiatric disorder without a diagnosis of organic illness. Conversion symptoms indicate a symptomatology related to voluntary motor or sensory functions, without physical signs or organic diseases, causing distress and impaired quality of life. In addition, the patient should show ambivalence in reporting of symptoms, histrionic personality characteristics, symptoms worsening due to stress or history of similar symptoms observed in others. Anniversary reactions are experienced when symptoms of autonomic arousal, without organic illness, began on the anniversary of a relevant personal event. Irritable mood is characterized by brief or prolonged unpleasant episodes of irritability which require an effort of control.

Demoralization is a state related to the perception of being unable to cope with some pressing problems and/or of lack of adequate support from others (helplessness) even though the individual maintains the ability to react. If hopelessness is present, the patient tends to feel of having failed to meet others' expectations and believes that there are no solutions for his/her problems. Finally, personality characteristics include Type A behavior (the tendency to be excessively involved in work or other activity, with a pervasive sense of urgency, motor-expressive features related to time pressure, presence of hostility, cynicism or irritability, speeding up physical and mental activities and/or high desire for achievement and competitiveness) and alexithymia (the inability to describe appropriately emotions or the tendency to describe details instead of feelings, lacking of rich fantasy life and/or unawareness of somatic reactions related to emotions with occasional inappropriate affective behaviors).

The semi-structured interview based on the Diagnostic Criteria for Psychosomatic Research revised is composed by a modular structure, with question referring to the past six or 12 months. The clinical interview has been shown to have a good inter-rater reliability, construct validity, and predictor validity (Galeazzi et al., 2004). The DCPR-R SSI allows to assess conditions often neglected by traditional nosography and may be administered in addition to DSM criteria (Cosci & Fava, 2016). This combination provided a better comprehension of patients' psychological profile across several medical setting (Galeazzi et al., 2004).

3.3.1.3 Structured interview, based on Sidorkiewicz instrument, for the assessment of adherence to pharmacological treatment

A structured interview for the assessment of adherence to pharmacological treatment based on the Sidorkiewicz Adherence tool (Sidorkiewicz et al., 2016) was also administered to hypertensive patients. The instrument developed by Sidorkiewicz and colleagues (2016) has shown an acceptable validity and reliability and may be administered in both hospitals and primary care setting.

According to the instrument structure (Sidorkiewicz et al., 2016), the interview is composed by five questions about drug discontinuation, skipping daily dose, temporary dose interruption, missing dose and schedule delays. Thus, six adherence levels may be detected:

- High drug adherence (No drug holidays, no missing doses and no schedule errors)
- Good drug adherence (No drug holidays and no missing doses; schedule errors ≥ 4 hours)
- Moderate drug adherence (No drug holidays; missing doses once or twice a month and/or schedule errors ≥ 12 hours)
- Poor drug adherence (Drug holidays for 2–3 days and/or missing doses ≥ 1/week)
- Very poor drug adherence (Systematically skipping a daily dose and/or drug holidays ≥ 6 days)
- Discontinuation (Drug discontinuation)

3.3.1.4 The PsychoSocial Index

The PsychoSocial Index (PSI; Sonino & Fava, 1998; Piolanti et al., 2016) is a self-report questionnaire with questions involving specific responses: most require a yes/no answer, others are rated on a 3-points Likert scale (from "Not at all" to "A great deal"). The final item concerning quality of life has five possible choices (from "Excellent" to "Awful").

The PSI covers an initial domain related to some sociodemographic and clinical data, such as routine information about medical and psychiatric history, subject's family, employment and habits. It provides information on some threats to health, for instance alcohol or drug use (Piolanti et al., 2016).

Further, the PsychoSocial Index includes several clinical dimensions (Piolanti et al., 2016):

- Stress: this section allows to assess perceived and objective stress, life events and chronic stress. It consists of 17 questions with a total score ranging from 0 to 17. The higher the scores the greater the level of stress.

- Well-being: this section evaluates different well-being areas including positive relations with others, environmental mastery and autonomy. The score ranges from 0 to 6.

- Psychological distress: this section encompasses several symptoms addressing sleep disturbances, somatization, irritability, depression and anxiety. The total score ranges from 0 to 45.

- Abnormal illness behavior: this section allows the assessment of hypochondriacal beliefs and bodily preoccupations with a total score ranging from 0 to 9.

- Quality of life: this issue is assessed by a simple direct question, with a score ranging from 0 to 4.

The PsychoSocial Index has been used in various clinical populations showing high sensitivity and discriminating different degrees of psychosocial impairment in different populations (Piolanti et al., 2016).

During the cross-sectional and longitudinal study, the Italian version of the PSI (Sonino & Fava, 1998) was administered with particular regard to the following clinical domains: Stress, Psychological distress, Well-being, and Quality of life.

#### 3.3.1.5 The Symptom Questionnaire

The Symptom Questionnaire (SQ; Benasi et al., 2020; Fava et al., 1983; Kellner, 1987), is a 92-item self-rating instrument composed by four total scales: depression, anxiety, somatization and hostility-irritability. Each scale can be subdivided into a subscale of symptoms (depressive symptoms, anxiety symptoms, somatic symptoms and hostility-irritability symptoms) and a subscale of well-being (contentment, relaxation, physical well-being and friendliness). Items require a yes/no or true/false answer. Each scale and subscale can be scored separately, with scores ranging from 0 to 17 for the symptom subscales, from 0 to 6 for the well-being subscales, and from 0 to 23 for the four main scales. For each total scale, higher scores indicate greater psychological distress while higher scores in the well-being subscales indicate lack of well-being. The Symptom Questionnaire has been found to be a sensitive instrument to detect change with a good predictive and concurrent validity (Benasi et al., 2020).

#### 3.3.1.6 The Mental Pain Questionnaire

Mental pain was recently described in the framework of psychosomatic medicine (Fava et al., 2017) as a unitary individual state of psychological and emotional suffering due to behavioral and cognitive processes. The concept of mental pain was also operationalized trough the identification of several indicators, including feeling of pain, feeling of heart brokenness, feeling of loss, feeling that pain is everywhere, feeling that pain is always with the individual, inability to understand the cause of pain, sense of emptiness, loss of meaning of life, helplessness, suicidal behaviors as an escape from the pain (Fava, 2016).

The Mental Pain Questionnaire (MPQ; Fava, 2016) is a self-rating 10-item instrument with a yes/no response format with higher scores indicating higher levels of mental pain and developed in the framework of the "measurement-based care", an approach which recommends to administer "easy-to-use" scales for both patients and clinicians (Bech, 2016). The questionnaire was developed according to clinimetric principles (Feinstein, 1982, 1983) and has shown good statistical and clinimetric properties (Svicher et al., 2019), including satisfactory, good discrimination and sensitivity.

#### 3.3.1.7 The Euthymia Scale

A specific definition of euthymia was provided by Fava and Bech (2016). According to the Authors, euthymia is a condition characterized by the absence of affective disorders as well as by the presence of psychological flexibility and stress resistance (Fava & Bech, 2016). Thus, a state of euthymia seems to include several characteristics (Fava & Bech, 2016):

- A lack of mood disorders that may be subsumed under diagnostic rubrics. If the individual reported a history of mood disturbance, he/she should be in full remission; whereas if the subjects experiences mood or anxious symptomatology, the symptoms tend to be short, associated with certain situations and do not have a significant impact on everyday life.

- The individual feels cheerful, calm, active, interested in things and his/her sleep is restorative.

- The subject shows flexibility trough balance and integration of psychic forces. Further, the subject displays actions and feeling guided by a unifying outlook on life as well as resistance to stress (resilience and anxiety or frustration tolerance).

The Euthymia Scale (ES; Fava & Bech, 2016) is a self-report rating questionnaire conceived according to the conceptualization of euthymia provided by Marie Jahoda (1958), who defined it as the individual's balance among psychic forces leading to great levels of resilience and tolerance to frustration, and the 5-item World Health Organization Well-Being Index (WHO-5; Topp et al.,

2015) frequently administered to assess psychological well-being. The questionnaire is composed by 10 items rated on a true/false and yes/no format. The higher the score, the higher the level of euthymia. Fava and Bech (2016) developed the Euthymia Scale focusing on the clinimetric approach (Fava et al., 2012, 2018) which recommends scalability, incremental validity and sensitivity as primary clinimetric parameters for the validation of a scale. Carrozzino and colleagues (2019) tested scalability (ability of each item to measure a specific symptom with symptoms assessed via the scale belonging to an underlying clinical dimension) and incremental validity (which refers to the unique contribution of a rating scale in the assessment and prediction of a specific clinical dimension) (Fava et al., 2012) of the Euthymia Scale. The questionnaire was found to be a valid measure for both psychological flexibility and psychological well-being and appears to be reliable according to clinimetric principles (Carrozzino et al., 2019).

#### 3.3.1.8 The Italian version of the Hong Psychological Reactance Scale

The Italian version of the Hong Psychological Reactance Scale (HPRS; Hong & Faedda, 1996; Hong & Page, 1989) is a 14-item questionnaire aimed to measure the individual tendency to experience psychological reactance, according to the concept defined by Hong and Page (1989). Questions are rated on a 5-points Likert scale (from "Strongly disagree" to "Strongly agree") with higher scores indicating greater levels of psychological reactance.

#### 3.3.1.9 The GOSPEL questionnaire

The GOSPEL is a self-report questionnaire developed by Giannuzzi and colleagues (2005, 2008) aimed to evaluate patients' lifestyle habits in the past six months, including physical activity, dietary habits, stress management as well as family lifestyle and support. Particularly, it provides information on several scales:

- Practiced physical activity: with five items assessing both frequency and type of physical activity on a Likert scale based on four points, two items with a yes/no answer format evaluating eventual practiced sport and one item assessing the overall self-reported physical activity level on a 4-point Likert scale. The total physical activity score, obtained from the sum of each item score, may range from 0 to 20.

- Dietary habits: ten items evaluate the frequency of consumption, in a week, of specific food and beverages included in the Mediterranean diet (i.e., cooked and raw vegetables, fruit, fish, olive and seed oil, butter, cheese, wine and coffee). Each item is measured on a 4-point Likert scale and the score ranges from 0 to 30. Further, three items assess the frequency of certain behaviors during meals, such as the tendency to regularly consume a complete meal, to eat slowly as well as the perception to consume a meal in a relaxed way. Each item is measured on a 4-point Likert scale with scores ranging from 0 to 9.

- Smoking habits: one item, on a Likert scale based on four points, evaluates the frequency of smoking habits with the eventual number of cigarettes in a day.

- Stress management: seven items measure frequency and type of several stress management behaviors at work or in everyday life. Higher scores indicate inadequate stress management abilities.

- Family lifestyle habits: this section allows to indicate who and how many family members follow inadequate lifestyle habits, including smoking, unbalanced diet, sedentary lifestyle or high stress levels.

- Family support: one item assesses individual perception of family support in choosing healthy lifestyle behaviors. The item is on a 4-point Likert scale and high score indicates more perceived family support.

### 3.3.2 *Validation study*

#### 3.3.2.1 The Italian version of the Hong Psychological Reactance Scale

The Italian version of the Hong Psychological Reactance Scale (HPRS; Hong & Faedda, 1996; Hong & Page, 1989) was administered for assessing individual levels of psychological reactance.

#### 3.3.2.2 The Mental Pain Questionnaire

The Mental Pain Questionnaire (MPQ; Fava, 2016) was used to assess mental pain levels.

#### 3.3.2.3 The Euthymia Scale

The Euthymia Scale (Fava & Bech, 2016) a 10-item self-rated scale using a true/false and yes/no format, was also administered to detect individual levels of euthymia.

#### 3.3.2.4 The PsychoSocial Index

The PsychoSocial Index (PSI; Piolanti et al., 2016; Sonino & Fava, 1998) was administered in order to assess stress, psychological distress, well-being and quality of life. During the validation study, the Italian version of the PSI (Piolanti et al., 2016; Sonino & Fava, 1998) was administered with particular regard to the following clinical domains: Stress, Psychological distress, Well-being, and Quality of life.

Cardiovascular variables (including hypertension grading and duration, possible organ damage, blood pressure values, absolute cardiovascular risk, cardiovascular and other comorbidities, glycaemia, creatinine, cholesterol, triglycerides, weight and body mass index) were assessed by the cardiologist at the time of the referral to the Arterial Hypertension Clinic of Internal Medicine Division at the Bufalini Hospital in Cesena according to the guidelines for hypertension management (Williams et al., 2018).

### 3.4 **Statistical analyses**

3.4.1 *Cross-sectional study*

Appropriate descriptive statistics were run for sociodemographic and cardiac data as well as for prevalence of psychosomatic syndromes, lifestyle behaviors, and mean scores on psychological variables. Comparisons between hypertensive patients and controls were also performed at baseline, using chi-squared tests and Student's t-tests for independent samples according to the type of variables.

The General Lineal Model, particularly Multivariate Analysis of Variance adjusted for confounding factors, was performed to compare subgroups (i.e., hypertensive patients vs normotensive participants; hypertensive patients with vs without allostatic overload) as to dimensional psychological measures (i.e., the CID anxiety, depression and total scales; the PSI stress, psychological distress, quality of life and well-being scales; the SQ anxiety, depression, somatization and hostility/irritability scales; psychological reactance, euthymia and mental pain). The nonparametric Mann-Whitney U test was used to compare subjects on those variables that did not satisfy the assumptions required to perform the Analysis of Variance (ANOVA). For all tests performed, the significance level was set at 0.05, two tailed.

Further, multiple linear regression, controlled for potential confounders (i.e., age and gender), was performed to identify the predictive role of psychological variables (DCPR-R syndromes, PsychoSocial Index, Symptom Questionnaire and CID-20 scales, psychological reactance) on adherence, lifestyle and cardiac variables (i.e., hypertension grading, absolute cardiovascular risk).

All analyses were conducted using SPSS 25 software (IBM, 2010).

3.4.2 *Longitudinal study*

Appropriate descriptive statistics were run for sociodemographic and cardiac data at follow-up, as well as for prevalence of psychosomatic syndromes, lifestyle behaviors, and mean scores on psychological variables.

Repeated Measures Analysis of Variance was carried out to compare hypertensive patients' scores on dimensional psychological measures (i.e., the CID anxiety, depression and total scales; the PSI stress, psychological distress and well-being scales; the SQ anxiety, depression, somatization and hostility/irritability scales; psychological reactance, euthymia and mental pain) over time (i.e., at 1-year follow-up vs at baseline).

The nonparametric Wilcoxon signed rank test was used to compare subjects when the assumptions required to perform the ANOVA were not satisfied.

For all tests performed, the significance level was set at 0.05, two tailed.

All analyses were conducted using SPSS 25 software (IBM, 2010).

3.4.3 *Validation study*

An exploratory factor analysis was performed to detect the empirical structure of the scale. Factors with eigenvalues equal or greater than 1.0 and factor loading coefficients equal or greater than .30 were considered. Items loading with more than one factor were assigned to factor with greater loading coefficient.

All analyses were conducted using SPSS 25 (IBM, 2010).

## 3.5 Results

### 3.5.1 *Cross-sectional study*

*Hypertensive patients vs control subjects.* Prevalence of psychosomatic syndromes and lifestyle variables as well as mean scores on dimensional psychological measures are reported in **Tables 2, 3** and **4**. The most frequently reported psychosomatic syndromes were allostatic overload (35.6%), alexithymia (21.2%) and Type A behavior (17.5%).

With regard to dimensional psychological measures (**Table 5**), hypertensive patients showed significantly higher levels of affective symptoms as indicated by the CID anxiety ($p < .05$), CID depression ($p < .001$), CID total ($p < .001$), SQ anxiety ($p < .001$), SQ depression ($p < .001$), SQ somatization ($p < .001$) and SQ hostility/irritability ($p < .05$) scales compared to controls. Furthermore, patients displayed significantly higher scores on PSI psychological distress scale ($p < .001$), greater psychological reactance ($p < .001$) and mental pain ($p < .001$) as well as lower scores of PSI well-being ($p < .001$) and euthymia ($p < .001$) than control subjects.

**Table 2.** Prevalence of psychosomatic syndromes and psychological reactance among hypertensive patients and controls

| *Psychosomatic syndromes and psychological reactance* | Hypertensive patients (n=80) | Normotensive controls (n=80) |
|---|---|---|
| | *n (%)* | *n (%)* |
| *DCPR-R* | | |
| Allostatic overload | 34 (42.5) | 23 (28.7) |
| Health anxiety | 11 (13.7) | 9 (11.2) |
| Nosophobia | 1 (1.2) | 1 (1.2) |
| Hypochondria | 1 (1.2) | 2 (2.5) |
| Thanatophobia | 0 (0) | 0 (0) |
| Illness denial | 19 (23.7) | 7 (8.7) |
| Somatization | 14 (17.5) | 11 (13.7) |
| Conversion symptoms | 4 (5) | 2 (2.5) |
| Anniversary reaction | 2 (2.5) | 1 (1.2) |
| Somatic symptoms secondary to a psychiatric disorder | 3 (3.7) | 1 (1.2) |
| Demoralization | 15 (18.7) | 12 (15) |
| Demoralization with hopelessness | 1 (1.2) | 0 (0) |
| Irritable mood | 5 (6.2) | 6 (7.5) |

| | | |
|---|---|---|
| Type A behavior | 11 (13.7) | 17 (21.5) |
| Alexithymia | 15 (18.7) | 19 (23.7) |
| *Hong Psychological Reactance Scale* | | |
| Presence of psychological reactance | 53 (66.2) | 29 (36.2) |
| Absence of psychological reactance | 27 (33.7) | 51 (63.7) |

**Table 3.** Prevalence of lifestyle variables among hypertensive patients and controls

| *Lifestyle variables* | Hypertensive patients (n=80) | Normotensive controls (n=80) |
|---|---|---|
| | *n (%)* | *n (%)* |
| *GOSPEL* | | |
| Global physical activity | | |
| Low | 53 (66.2) | 30 (37.5) |
| Moderate | 21 (26.5) | 39 (48.7) |
| High | 4 (5) | 11 (13.7) |
| Very high | 2 (2.5) | 0 (0) |
| Cooked vegetable consumption | | |
| Never or occasionally | 6 (7.5) | 12 (15) |
| Twice a week | 12 (15) | 35 (43.7) |
| Once a day | 39 (48.7) | 23 (28.7) |
| More than once a day | 23 (28.7) | 10 (12.5) |
| Raw vegetable consumption | | |
| Never or occasionally | 5 (6.2) | 13 (16.2) |
| Twice a week | 9 (11.2) | 24 (30) |
| Once a day | 42 (52.5) | 26 (32.5) |
| More than once a day | 24 (30) | 17 (21.2) |
| Fruit consumption | | |
| Never or occasionally | 5 (6.2) | 4 (5) |
| Twice a week | 14 (17.5) | 16 (20) |
| Once a day | 37 (46.2) | 37 (46.2) |
| More than once a day | 24 (30) | 23 (28.7) |
| Fish consumption | | |

| | | |
|---|---|---|
| Never or occasionally | 15 (18.7) | 21 (26.2) |
| Once a week | 30 (37.5) | 25 (31.2) |
| Twice a week | 25 (31.2) | 33 (41.2) |
| More than twice a week | 10 (12.5) | 1 (1.2) |
| Olive oil consumption | | |
| Never | 0 (0) | 0 (0) |
| Sometimes | 2 (2.5) | 6 (7.5) |
| Often | 3 (3.7) | 13 (16.2) |
| Regularly | 75 (93.7) | 61 (76.2) |
| Seed oil consumption | | |
| Never | 64 (80) | 52 (65) |
| Sometimes | 14 (17.5) | 26 (32.5) |
| Often | 1 (1.2) | 1 (1.2) |
| Regularly | 1 (1.2) | 1 (1.2) |
| Butter consumption | | |
| Never | 60 (7) | 52 (65) |
| Sometimes | 19 (23.7) | 26 (32.5) |
| Often | 1 (1.2) | 2 (2.5) |
| Regularly | 0 (0) | 0 (0) |
| Cheese consumption | | |
| Never | 6 (7.5) | 6 (7.5) |
| Sometimes | 31 (38.7) | 25 (31.2) |
| Often | 39 (48.7) | 37 (46.2) |
| Regularly | 4 (5) | 12 (15) |
| Wine consumption | | |

| | | |
|---|---|---|
| Never or occasionally | 43 (53.7) | 50 (62.5) |
| Half l/die or less | 37 (46.2) | 27 (33.7) |
| 1 l/die or less | 0 (0) | 3 (3.7) |
| More than 1 l/die | 0 (0) | 0 (0) |
| Coffee consumption | | |
| Never or occasionally | 16 (20) | 14 (17.5) |
| 1 cup/die | 27 (33.7) | 21 (26.2) |
| 2-4 cups/die | 34 (42.5) | 42 (52.5) |
| 5 cups/die or more | 3 (3.7) | 3 (3.7) |

**Table 4.** Mean scores on dimensional psychological measures among hypertensive patients and controls

| *Psychological measures* | Hypertensive patients (n=80) | Normotensive controls (n=80) |
|---|---|---|
| | *Mean (SD)* | *Mean (SD)* |
| *Clinical Interview for Depression* | | |
| Anxiety | 6.89 (2.43) | 5.89 (1.80) |
| Depression | 15.69 (3.92) | 13.22 (2.81) |
| Total | 33.12 (7.1) | 28.35 (4.79) |
| *Psychosocial Index* | | |
| Stress | 2.83 (1.75) | 3.00 (1.44) |
| Psychological distress | 11.33 (6.14) | 5.66 (4.18) |
| Well-being | 4.78 (0.89) | 8.15 (1.60) |
| Quality of life | 2.92 (0.72) | 2.94 (0.70) |
| *Symptom Questionnaire* | | |
| Anxiety | 6.76 (4.66) | 3.42 (2.68) |
| Depression | 4.17 (3.66) | 2.32 (2.35) |
| Somatization | 8.28 (4.22) | 3.42 (3.45) |
| Hostility/Irritability | 4.12 (3.68) | 2.73 (2.59) |
| *Hong Psychological Reactance Scale* | 2.36 (0.92) | 1.79 (0.95) |
| *Euthymia Scale* | 6.29 (2.31) | 8.71 (1.43) |
| *Mental Pain Questionnaire* | 3.09 (2.39) | 1.27 (1.74) |

**Table 5.** Differences between hypertensive patients and controls on dimensional psychological measures at baseline

| *Psychological measures* | Hypertensive patients (n=80) | Normotensive controls (n=80) | |
|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *p* |
| *Clinical Interview for Depression* | | | |
| Anxiety | 6.89 (2.43) | 5.89 (1.80) | **.006**** |
| Depression | 15.69 (3.92) | 13.22 (2.81) | **<.001**** |
| Total | 33.12 (7.09) | 28.35 (4.79) | **<.001**** |
| *PsychoSocial Index* | | | |
| Stress | 2.83 (1.75) | 3.00 (1.44) | .522 |
| Psychological distress | 11.34 (6.14) | 5.66 (4.18) | **<.001**** |
| Well-being | 4.79 (0.89) | 8.15 (1.60) | **<.001**** |
| Quality of life | 2.92 (0.72) | 2.93 (0.71) | .912 |
| *Symptom Questionnaire* | | | |
| Anxiety | 6.76 (4.66) | 3.42 (2.68) | **<.001**** |
| Depression | 4.17 (3.66) | 2.32 (2.35) | **<.001**** |
| Somatization | 8.28 (4.22) | 3.42 (3.45) | **<.001**** |
| Hostility/Irritability | 4.12 (3.68) | 2.73 (2.59) | **.013**** |
| *Hong Psychological Reactance Scale* | 2.36 (0.92) | 1.79 (0.95) | **<.001*** |
| *Euthymia Scale* | 6.29 (2.31) | 8.71 (1.43) | **<.001**** |
| *Mental Pain Questionnaire* | 3.09 (2.39) | 1.27 (1.74) | **<.001**** |

** p value < .05 (obtained using the Multivariate Analysis of Variance); ** p value < .05 (obtained using the Mann Whitney U test)*

*Hypertensive patients with and without allostatic overload.* At baseline, thirty-four hypertensive patients (42.5%) displayed allostatic overload according to clinimetric criteria. When comparing patients with and without allostatic overload, significant differences were found as to gender ($\chi2$=7.020, $p < .01$) and adherence to pharmacological treatment ($\chi2$=11.586, $p < .05$) (**Table 6**).

Hypertensive patients with allostatic overload displayed significantly higher scores on CID depression ($p < .001$), CID anxiety ($p < .001$) and CID total scales ($p < .001$). Significantly higher scores on PSI stress ($p < .001$) and PSI psychological distress ($p < .05$) were also reported compared to patients without allostatic overload. Further, the presence of allostatic overload appeared to be associated with significantly higher levels of SQ anxiety, SQ depression, SQ somatization and SQ hostility/irritability ($p < .05$), as well as with greater mental pain ($p < .05$), and lower levels of euthymia ($p < .05$), PSI well-being ($p < .001$) and PSI quality of life ($p < .001$) (**Table 7**).

Multiple logistic regression models revealed that hypertensive patients with illness denial were more likely to report poor adherence to pharmacological treatment ($\chi2$= 156.441, $p < .05$; OR=1.510, $p < .05$, 95%CI 2.180-10.458). Further, patients with illness denial were less likely to eat cooked ($\chi2$= 145.852, $p < .001$; OR=.005, $p < .05$, 95%CI 6.60-.421) and raw veggies ($\chi2$= 130.160, $p < .001$; OR=.008, $p < .05$, 95%CI .000-.459), whereas patients with higher levels of affective symptomatology (based on Symptom Questionnaire and Clinical Interview for Depression scores) were less likely to eat cooked veggies ($\chi2$= 145.852, $p < .001$; OR=.442, $p < .05$, 95%CI .199-.981) and fruit ($\chi2$= 102.505, $p < .05$; OR=.514, $p < .05$, 95%CI .268-.986).

**Table 6.** Differences between hypertensive patients with and without AO as to sociodemographic and clinical characteristics

| *Sociodemographic and clinical variables* | Presence of AO (n=34) | Absence of AO (n=46) | | |
|---|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *t* | *p* |
| Age (years) | 53.85 (10.70) | 56.26 (8.46) | .916 | .342 |
| | *n (%)* | *n (%)* | *χ2* | *p* |
| Gender | | | 7.020 | **.008*** |
| Male | 12 (35.3) | 30 (65.2) | | |
| Female | 22 (64.7) | 16 (34.8) | | |
| Educational level | | | 5.355 | .148 |
| Primary school | 2 (5.9) | 0 (0) | | |
| Secondary school | 15 (44.1) | 14 (30.4) | | |
| High school | 15 (44.1) | 30 (65.2) | | |
| Degree or more | 2 (5.9) | 2 (4.3) | | |
| Marital status | | | 1.658 | .798 |
| Not married | 8 (23.5) | 8 (17.4) | | |
| Married | 24 (70.6) | 33 (71.7) | | |
| Divorced/Separated | 2 (5.9) | 4 (8.7) | | |
| Widow | 0 (0) | 1 (2.2) | | |
| Occupational status | | | 1.196 | .274 |
| Employed | 24 (70.6) | 27 (58.7) | | |
| Retired/Unemployed | 10 (29.4) | 19 (41.3) | | |
| Physical comorbidities | 12 (35.3) | 10 (21.7) | 1.802 | .180 |

| | | | | |
|---|---|---|---|---|
| Psychiatric comorbidities | 8 (23.5) | 7 (15.2) | .887 | .346 |
| Current psychotropic medications | 8 (23.5) | 10 (21.7) | .036 | .850 |
| Past hospitalization | 24 (70.6) | 33 (71.3) | .013 | .910 |
| Allergies | 9 (26.5) | 5 (10.9) | 3.296 | .069 |
| Smoking | 6 (17.6) | 12 (26.1) | .799 | .372 |
| Alcohol consumption | 2 (5.9) | 3 (6.5) | .014 | .907 |
| Adherence | | | 11.586 | **.021*** |
| High | 21 (61.8) | 25 (54.3) | | |
| Good | 0 (0) | 6 (13) | | |
| Moderate | 1 (2.9) | 8 (17.4) | | |
| Poor | 10 (29.4) | 6 (13) | | |
| Very poor | 2 (5.9) | 1 (2.2) | | |
| Hypertension grading | | | 8.411 | .078 |
| High normal | 6 (17.6) | 0 (0) | | |
| Grade 1 | 23 (67.6) | 27 (58.7) | | |
| Grade 2 | 3 (8.8) | 4 (8.7) | | |
| Grade 3 | 0 (0) | 1 (2.2) | | |
| Isolated systolic hypertension | 1 (2.9) | 3 (6.5) | | |
| Absolute cardiovascular risk | | | 2.870 | .580 |
| Low | 11 (32.3) | 17 (36.9) | | |
| Moderate | 10 (29.4) | 10 (21.7) | | |

| | | | | |
|---|---|---|---|---|
| High | 6 (17.6) | 7 (15.2) | | |
| Very high | 0 (0) | 3 (6.5) | | |
| Weight status | | | 1.636 | .441 |
| Normal weight | 15 (44.1) | 14 (30.4) | | |
| Overweight | 9 (26.5) | 17 (36.9) | | |
| Obesity | 6 (17.6) | 8 (17.4) | | |
| Abdominal obesity | 1 (2.9) | 6 (13) | 2.143 | .143 |
| Family history of CVD | 7 (20.6) | 6 (13) | .838 | .360 |
| | *Mean (SD)* | *Mean (SD)* | *t* | *p* |
| Resting heart rate (BPM) | 76.90 (11.57) | 74.17 (11.83) | .079 | .343 |
| Systolic (mmHg) | 138.92 (12.30) | 139.10 (13.55) | 1.579 | .957 |
| Diastolic (mmHg) | 82.42 (8.99) | 83.51 (7.86) | .931 | .602 |
| | *n (%)* | *n (%)* | $\chi 2$ | *p* |
| Duration of illness | | | .304 | .581 |
| 12 months or more | 28 (82.3) | 36 (78.2) | | |
| Less than 12 months | 5 (14.7) | 9 (19.5) | | |
| Organ damage | 9 (26.5) | 11 (23.9) | .178 | .915 |
| History of CVD | 3 (8.8) | 4 (8.7) | .003 | .956 |
| Diabetes | | | 1.537 | .464 |
| Type 1 | 0 (0) | 1 (2.2) | | |
| Type 2 | 2 (5.8) | 1 (2.2) | | |
| Hyperglycemia | 1 (2.9) | 4 (8.7) | .903 | .342 |

| | | | | |
|---|---|---|---|---|
| Hypercholesterolemia | 2 (5.8) | 8 (17.4) | 1.577 | .209 |
| Hypertriglyceridemia | 0 (0) | 4 (8.7) | 2.810 | .094 |
| | *Mean (SD)* | *Mean (SD)* | *t* | *p* |
| Glycaemia | 99.35 (24.13) | 103.70 (24.00) | .002 | .523 |
| Creatinine | .86 (.24) | .91 (.14) | 7.200 | .487 |
| Total cholesterol | 185.57 (25.74) | 200.78 (36.08) | 1.326 | .095 |
| HDL cholesterol | 57.65 (14.48) | 61.93 (28.86) | 1.814 | .540 |
| LDL cholesterol | 115.15 (20.58) | 116.23 (36.54) | 3.807 | .910 |
| Triglyceride | 128.21 (85.15) | 134.83 (72.40) | .053 | .764 |

**p value < 0.05; AO: allostatic overload; CVD: cardiovascular diseases*

**Table 7.** Differences between hypertensive patients with and without AO on dimensional psychological measures at baseline

| *Psychological measures* | Presence of AO (n=34) | Absence of AO (n=46) | |
|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *p* |
| *Clinical Interview for depression* | | | |
| Anxiety | 6.35 (2.64) | 7.40 (1.97) | **<.001**** |
| Depression | 17.87 (3.99) | 14.30 (3.10) | **<.001*** |
| Total | 36.63 (5.84) | 30.30 (6.13) | **<.001*** |
| *Psychosocial Index* | | | |
| Stress | 3.63 (1.57) | 1.97 (1.16) | **<.001**** |
| Psychological distress | 13.97 (5.58) | 9.59 (5.54) | **<.05*** |
| Well-being | 4.30 (0.95) | 5.24 (0.55) | **<.001**** |
| Quality of life | 2.50 (0.73) | 3.27 (0.51) | **<.001**** |
| *Symptom Questionnaire* | | | |
| Anxiety | 9.30 (4.32) | 5.03 (3.93) | **<.001*** |
| Depression | 6.07 (4.22) | 2.75 (1.92) | **<.001**** |
| Somatization | 10.07 (3.88) | 7.49 (4.17) | **<.05*** |
| Hostility/Irritability | 5.67 (4.06) | 2.97 (2.93) | **<.05**** |
| *Hong Psychological Reactance Scale* | 1.77 (0.97) | 1.70 (0.91) | .782 |
| *Euthymia Scale* | 5.23 (1.87) | 7.16 (2.30) | **<.05**** |
| *Mental Pain Questionnaire* | 3.73 (2.32) | 2.57 (2.35) | **<.05*** |

*AO: allostatic overload; * p value < .05 (obtained using the Multivariate Analysis of Variance); **p value < .05 (obtained using the Mann Whitney U test)*

3.5.2 *Longitudinal study*

Data (n=38) on prevalence of psychosomatic syndromes, lifestyle behaviors, and means scores on dimensional psychological variables are reported in **Tables 8, 9** and **10**. The most frequently reported psychosomatic syndromes at one year follow-up were allostatic overload (36.8%), persistent somatization (21%) and illness denial (18.4%).

As to dimensional psychological measures at follow-up (**Table 11**), patients showed significantly lower levels of PSI stress ($p < .05$) and mental pain ($p < .05$) compared to baseline. They also displayed significantly higher scores in PSI well-being scale ($p < .001$). However, at follow-up, patients reported significantly lower scores of PSI quality of life ($p < .001$).

**Table 8.** Prevalence of psychosomatic syndromes and psychological reactance among hypertensive patients assessed at baseline and 1-year follow-up

| *Psychosomatic syndromes and psychological reactance* | Hypertensive patients assessed at baseline (n=38) | Hypertensive patients assessed at follow-up (n=38) |
|---|---|---|
| | *n (%)* | *n (%)* |
| *DCPR-R* | | |
| Allostatic overload | 15 (39.5) | 14 (36.8) |
| Health anxiety | 5 (13.1) | 2 (5.3) |
| Nosophobia | 1 (2.7) | 0 (0) |
| Hypochondria | 0 (0) | 1 (2.7) |
| Thanatophobia | 0 (0) | 0 (0) |
| Illness denial | 9 (23.7) | 7 (18.4) |
| Somatization | 8 (21) | 8 (21) |
| Conversion symptoms | 2 (5.3) | 0 (0) |
| Anniversary reaction | 2 (5.3) | 0 (0) |

| | | |
|---|---|---|
| Somatic symptoms secondary to a psychiatric disorder | 1 (2.7) | 0 (0) |
| Demoralization | 6 (15.8) | 6 (15.8) |
| Demoralization with hopelessness | 0 (0) | 0 (0) |
| Irritable mood | 3 (7.9) | 3 (7.9) |
| Type A behavior | 4 (10.5) | 3 (7.9) |
| Alexithymia | 10 (26.3) | 5 (13.1) |
| | *n (%)* | *n (%)* |
| *Hong Psychological Reactance Scale* | | |
| Presence of psychological reactance | 16 (42.1) | 9 (23.7) |
| Absence of psychological reactance | 22 (57.9) | 29 (76.3) |

**Table 9.** Prevalence of lifestyle variables among hypertensive patients assessed at baseline and 1-year follow-up

| *Lifestyle variables* | Hypertensive patients assessed at baseline (n=38) | Hypertensive patients assessed at follow-up (n=38) |
|---|---|---|
| | *n (%)* | *n (%)* |
| *GOSPEL* | | |
| Global physical activity | | |
| Low | 21 (55.3) | 29 (76.3) |
| Moderate | 13 (34.2) | 7 (18.4) |
| High | 2 (5.3) | 2 (5.3) |
| Very high | 2 (5.3) | 0 (0) |
| Cooked vegetable consumption | | |
| Never or occasionally | 6 (15.8) | 0 (0) |
| Twice a week | 8 (21) | 4 (10.5) |
| Once a day | 16 (42.1) | 18 (47.4) |
| More than once a day | 8 (21) | 16 (42.1) |
| Raw vegetable consumption | | |
| Never or occasionally | 5 (13.1) | 0 (0) |
| Twice a week | 7 (18.4) | 5 (13.1) |
| Once a day | 18 (47.4) | 17 (44.7) |
| More than once a day | 8 (21) | 16 (42.1) |
| Fruit consumption | | |
| Never or occasionally | 4 (10.5) | 0 (0) |
| Twice a week | 9 (23.7) | 4 (10.5) |
| Once a day | 14 (36.8) | 18 (47.4) |

| | | |
|---|---|---|
| More than once a day | 11 (29) | 16 (42.1) |
| Fish consumption | | |
| Never or occasionally | 11 (29) | 4 (10.5) |
| Once a week | 12 (31.6) | 18 (47.4) |
| Twice a week | 12 (31.6) | 15 (39.5) |
| More than twice a week | 3 (7.9) | 1 (2.6) |
| Olive oil consumption | | |
| Never | 0 (0) | 0 (0) |
| Sometimes | 1 (2.6) | 0 (0) |
| Often | 1 (2.6) | 1 (2.6) |
| Regularly | 36 (94.7) | 37 (97.4) |
| Seed oil consumption | | |
| Never | 29 (76.3) | 31 (81.6) |
| Sometimes | 7 (18.4) | 6 (15.8) |
| Often | 1 (2.6) | 1 (2.6) |
| Regularly | 1 (2.6) | 0 (0) |
| Butter consumption | | |
| Never | 27 (71) | 26 (68.4) |
| Sometimes | 11 (28.9) | 12 (31.6) |
| Often | 0 (0) | 0 (0) |
| Regularly | 0 (0) | 0 (0) |
| Cheese consumption | | |
| Never | 3 (7.9) | 0 (0) |
| Sometimes | 16 (42.1) | 27 (71) |
| Often | 17 (44.7) | 11 (28.9) |

| | | |
|---|---|---|
| Regularly | 2 (5.3) | 0 (0) |
| Wine consumption | | |
| Never or occasionally | 23 (60.5) | 26 (68.4) |
| Half l/die or less | 15 (39.5) | 12 (31.6) |
| 1 l/die or less | 0 (0) | 0 (0) |
| More than 1 l/die | 0 (0) | 0 (0) |
| Coffee consumption | | |
| Never or occasionally | 11 (28.9) | 14 (36.8) |
| 1 cup/die | 12 (31.6) | 8 (21) |
| 2-4 cups/die | 13 (34.2) | 16 (42.1) |
| 5 cups/die or more | 2 (5.3) | 0 (0) |

**Table 10.** Mean scores on dimensional psychological measures among hypertensive patients assessed at baseline and 1-year follow-up

| *Psychological measures* | Hypertensive patients assessed at baseline (n=38) | Hypertensive patients assessed at follow-up (n=38) |
|---|---|---|
| | *Mean (SD)* | *Mean (SD)* |
| *Clinical Interview for Depression* | | |
| Anxiety | 7.10 (2.42) | 6.42 (2.20) |
| Depression | 14.79 (3.07) | 14.86 (4.24) |
| Total | 31.95 (5.84) | 32.05 (7.91) |
| *Psychosocial Index* | | |
| Stress | 2.81 (1.49) | 2.24 (1.23) |
| Psychological distress | 11.02 (6.49) | 10.62 (6.11) |
| Well-being | 4.59 (.97) | 7.35 (1.49) |
| Quality of life | 2.88 (.65) | 2.38 (.76) |
| *Symptom Questionnaire* | | |
| Anxiety | 5.90 (3.99) | 7.36 (4.21) |
| Depression | 3.41 (2.88) | 3.74 (2.55) |
| Somatization | 8.28 (4.11) | 8.69 (4.50) |
| Hostility/Irritability | 3.97 (3.83) | 4.49 (3.78) |
| *Euthymia Scale* | 6.10 (2.12) | 6.39 (3.43) |
| *Mental Pain Questionnaire* | 2.71 (2.37) | 1.32 (1.55) |

**Table 11.** Differences among hypertensive patients assessed at baseline at 1-year follow-up on dimensional psychological measures

| *Psychological measures* | Baseline assessment (n=38) | Follow-up assessment (n=38) | |
|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *p* |
| *Clinical Interview for depression* | | | |
| Anxiety | 7.10 (2.42) | 6.42 (2.20) | .066 |
| Depression | 14.79 (3.07) | 14.86 (4.24) | .911 |
| Total | 31.95 (5.84) | 32.05 (7.91) | .925 |
| *Psychosocial Index* | | | |
| Stress | 2.81 (1.49) | 2.24 (1.23) | **.049**** |
| Psychological distress | 11.02 (6.49) | 10.62 (6.11) | .710 |
| Well-being | 4.59 (.97) | 7.35 (1.49) | **< .001*** |
| Quality of life | 2.88 (.65) | 2.38 (.76) | **<.001*** |
| *Symptom Questionnaire* | | | |
| Anxiety | 5.90 (3.99) | 7.36 (4.21) | .060 |
| Depression | 3.41 (2.88) | 3.74 (2.55) | .419 |
| Somatization | 8.28 (4.11) | 8.69 (4.50) | .580 |
| Hostility/Irritability | 3.97 (3.83) | 4.49 (3.78) | .551 |
| *Hong Psychological Reactance Scale* | 1.84 (.94) | 1.47 (.86) | .080 |
| *Euthymia Scale* | 6.10 (2.12) | 6.39 (3.43) | .426 |
| *Mental Pain Questionnaire* | 2.71 (2.37) | 1.32 (1.55) | **.021**** |

** p value < .05 (obtained using the Repeated Measures Analysis of Variance); ** p value < .05 (obtained using the Wilcoxon signed rank test)*

3.5.3 *Validation study*

An exploratory factor analysis was performed to test the empirical structure of the Hong Psychological Reactance Scale. Principal components extraction method and an oblique rotation were carried out. The feasibility of factor analysis was confirmed by a KMO coefficient value of .754 and a significant Bartlett's test ($\chi2(91)=593.5$; $p < .001$). The pattern matrix (representing the rotated factor structure) showed a four-factor structure (**Table 12**). Internal consistency values for each factor were, respectively, .72, .66, .50 and .65. As convergent validity, the HPRS four-factor structure found was correlated with mental pain ($r = .48$; $p < .01$) and psychological distress ($r = .45$; $p < .01$). Further, negative correlations with euthymia ($r = -.56$; $p < .01$) and well-being ($r = -.41$; $p < .01$) were also found.

**Table 12.** Exploratory factor analysis pattern matrix

| | *Factors* | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Item 1 | ,290 | | **,369** | ,343 |
| Item 2 | **,541** | ,459 | -,213 | -,199 |
| Item 3 | | **,587** | ,169 | ,107 |
| Item 4 | | **,374** | ,339 | ,132 |
| Item 5 | -,345 | ,288 | ,201 | **,747** |
| Item 6 | -,121 | | **,914** | |
| Item 7 | ,250 | | | **,673** |
| Item 8 | ,398 | | **,597** | |
| Item 9 | | **,758** | -,160 | ,436 |
| Item 10 | **,758** | | | ,151 |
| Item 11 | ,114 | **,518** | ,106 | -,216 |
| Item 12 | ,200 | -,100 | -,205 | **,835** |
| Item 13 | **,700** | | ,170 | ,129 |
| Item 14 | ,277 | **-,470** | ,329 | ,374 |

Oblique rotation (Oblimin with Kaiser Normalization) on Principal Component Extraction.

## 3.6 Discussion

### 3.6.1 *Cross-sectional study*

The aim of this cross-sectional study was to evaluate the predictive role of psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, well-being and quality of life on adherence to antihypertensive medications, lifestyle habits, hypertension severity and absolute cardiovascular risk grading in a sample of hypertensive patients compared to normotensive controls. Further, we expected to identify subgroups of patients with essential hypertension characterized by specific psychological profiles.

The present study was characterized by the use of an innovative and comprehensive assessment strategy based on clinimetric tools administered in the setting of cardiovascular diseases and providing new data on the role of psychosocial factors in hypertension.

In our sample, significantly greater psychological distress levels have been found in patients with essential hypertension compared to normotensive individuals, as revealed by both clinical interviews and self-rating scales scores. More specifically, hypertensive patients reported significantly higher levels of depressive and anxiety symptoms as well as somatic complaints and mental pain. These results confirm those reported in a previous study conducted on hypertensive patients assessed with clinimetric instruments (Guidi et al., 2020) and additional studies carried out on cardiovascular patients (Hamieh et al., 2020; Liu et al., 2017; Maatouk et al., 2016; Ojike et al., 2016). Depressive and anxiety symptomatology have been shown to be frequently reported in patients with chronic diseases, including arterial hypertension, and have been associated with adverse health outcomes and cardiovascular issues (Johnson, 2019; Scalco et al., 2005).

Further, in this study, patients with essential hypertension also displayed greater levels of hostility/irritability and psychological reactance when compared to controls. According to Yan and colleagues (2003) hostility appears to be positively associated with high blood pressure incidence and has been shown to represent an independent risk factor for coronary heart disease (Miller et al.,

1996) and all-cause mortality in cardiac setting (Boyle et al., 2005; Siegler et al., 1992). As to psychological reactance, defined as a motivational state aimed to restore the perception of autonomy when individual freedom is threatened (Brehm, 1966, 1972; Brehm & Brehm, 1981), a previous study conducted by Abel and Barksdale (2012) has reported that psychological reactance was found to be present in hypertensive patients and suggested that this construct may have a role in contributing to poor adherence levels in this type of clinical population.

According to literature, psychological well-being appears to promote a better cardiovascular health (Boehm & Kubzansky, 2012; Kubzansky et al., 2018¸ Trudel-Fitzgerald et al., 2014). Further, as reported by previous studies, psychological well-being has been shown to consistently protect against several cardiovascular issues (Boehm & Kubzansky, 2012) and to be negatively associated with high blood pressure levels (Hildingh & Baigi, 2010; Trudel-Fitzgerald et al., 2014). Similarly, in our study, hypertensive patients also displayed significantly lower levels of self-rated psychological well-being and euthymia than controls, suggesting the protective role of psychological well-being to cardiovascular system (Boehm & Kubzansky, 2012; Kubzansky et al., 2018; Trudel-Fitzgerald et al., 2014).

In the present study, allostatic overload was found to be the most frequently reported psychosomatic syndrome among hypertensive patients (42.5%), supporting its role in the onset and clinical progression of essential hypertension (Mocayar-Maron et al., 2019).

In line with the results of a recent study (Guidi et al., 2020), the presence of allostatic overload among hypertensive patients appeared to be significantly related to higher levels of psychological distress. Particularly, hypertensive patients displaying allostatic overload showed significantly greater levels of depression, anxiety, stress, distress, somatization, hostility/irritability and mental pain, when compared to hypertensive patients without allostatic overload. These findings are in accordance to several previous studies (Gostoli et al., 2016; Guidi et al., 2016; Offidani et al., 2013; Porcelli et al., 2012) conducted in cardiac populations using clinimetric assessment methods. Furthermore, a recent systematic review (Guidi et al., 2021) also pointed out the link between allostatic load and overload with cardiovascular diseases, including essential hypertension. Thus, results of the present cross-sectional study appear to confirm the role of allostatic overload in the field of cardiovascular health.

Hypertensive patients with allostatic overload in our sample, also displayed lower levels of euthymia, psychological well-being and quality of life, compared to those without allostatic overload. These findings are in line with those reported by Piolanti and collaborators (2019) in a study conducted on primary care patients where allostatic overload was not only the most frequently psychosomatic syndrome reported but has been found to be associated with significantly lower levels of psychological well-being and quality of life.

Regression analysis models revealed that hypertensive patients displaying illness denial, the tendency to do not admit the presence or severity of the illness (Fava et al., 2017), were more likely to report poor adherence levels to pharmacological treatment. This seems to be particularly relevant when considering average adherence rates towards antihypertensive medications. According to the most recent guidelines for the management of arterial hypertension (Williams et al., 2018), studies considering urine or blood assays have reported low rates of treatment adherence in hypertensive patients. Further, approximately 50-70% of patients seem to do not follow the prescribed treatments (Mant & McManus, 2006). A lack of adherence to pharmacological treatment may cause hypertension-related morbidity and mortality as well as unnecessary overprescription and disease worsening (Mazzaglia et al., 2009; Ogden et al., 2000).

Further, in the present study, hypertensive patients reporting illness denial, as well as patients reporting higher scores on Symptom Questionnaire and Clinical Interview for Depression, were less likely to consume and include fruit and vegetables in their usual diet. As reported by previous studies (Appel et al., 2006; Chobanian et al., 2003; Dickinson et al., 2006; Estruch et al., 2018; Mente et al., 2009; Sofi et al., 2010) following a balanced diet may prevent the onset of essential hypertension in healthy individuals and may improve blood pressure values control in hypertensive patients. Dietary habits of patients with arterial hypertension should be characterized by a regular and balanced consumption of vegetables, legumes, fruit, low-fat dairy products, fish and unsaturated fats (Dickinson et al., 2006; Mente et al., 2009; Sofi et al., 2010). In fact, the Mediterranean diet may reduce the risk of cardiovascular events and all-cause mortality (Dickinson et al., 2006; Estruch et al., 2018; Mente et al., 2009; Sofi et al., 2010) and appears to significantly reduce ambulatory blood pressure, blood glucose and lipid levels (Doménech et al., 2014).

The latter results from our study support the association between illness denial and increased risk of reporting poor adherence to pharmacological treatment among hypertensive patients, as well as a significant association between illness denial and affective symptomatology with unbalanced diet. Further, these findings highlight the clinical relevance of the associations between DCPR diagnoses (i.e., allostatic overload and illness denial) and clinical variables confirming those reported in a recent cross-sectional study (Guidi et al., 2020) and allowing to detect psychosocial factors modifiable by psychosocial interventions tailored to individual needs (Rosemberg et al., 2020).

No significant association were found between psychosocial factors (i.e., psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, well-being and quality of life) and hypertension grading or absolute cardiovascular risk. This may be due to the fact that the majority of hypertensive patients (65%) have been reported high adherence levels to prescribed antihypertensive medications as well as acceptable lifestyle habits.

### 3.6.2 *Longitudinal study*

A longitudinal study was carried out with the aim to evaluate the temporal stability of psychosomatic syndromes, affective symptomatology, psychological reactance, psychological distress, well-being and quality of life, at one-year follow-up.

In line with the results of the cross-sectional study, allostatic overload was the most frequently reported psychosomatic syndrome among hypertensive patients at one year follow-up, confirming the impact of chronic psychosocial stressors on progression and maintenance of arterial hypertension (Mocayar Maròn et al., 2019). Other psychosomatic syndromes frequently reported among the same clinical sample at one year follow-up were persistent somatization and illness denial, supporting the temporal stability of DCPR diagnoses. These latter syndromes belong to the clinical spectrum of illness behavior (Fava et al., 2017), which may be linked to elevated blood pressure values, as suggested by a recent study conducted on patients with essential hypertension (Guidi et al., 2020).

In the present study, hypertensive patients have been shown significantly lower levels of stress and mental pain as well as significantly higher levels of psychological well-being in comparison to baseline evaluations. High adherence rates to pharmacological prescriptions and healthy lifestyle behaviors may have contributed to this improvement. As reported by Williams and colleagues (2018), high adherence rates to pharmacological treatment appear to be crucial in order to avoid disease worsening or cardiovascular complications. Further, it is also widely recognized that adequate lifestyle habits may have a role in preventing the onset or delaying the clinical progression of hypertension, reducing both blood pressure levels and cardiovascular risk (Mancia et al., 2013; Piepoli et al., 2016; Winnicki et al., 2006) and allowing dosage reductions of antihypertensive medications (Mahmood et al., 2019).

Finally, in our study, hypertensive patients reported significantly lower levels of quality of life at one year follow-up. This finding may be explained considering the effects of the COVID-19 outbreak. In addition to physical health and economic issues, the pandemic as well as the measures taken to control its spread, had and are still having a huge and detrimental impact on many levels, particularly in the field of mental health (Chen et al., 2021; Fiorillo & Gorwood, 2020; Lindert et al., 2021; Sheridan Rains et al., 2021). Periods of mandatory quarantine, lack of social contacts, health concerns as well as uncertainty about the future, may contribute to or exacerbate mental health problems (Chen et al., 2021; Fiorillo & Gorwood, 2020; Lindert et al., 2021). Further, according to literature, the pandemic also affected individual quality of life in both general and clinical population (Chalhub et al., 2021; Ferreira et al., 2021; Hu et al., 2021). As to hypertension, a cross-sectional study conducted by Sekerci and Yildirimturk (2020) reported that hypertensive patients have displayed low scores of quality of life during COVID-19 pandemic, supporting our findings.

3.6.3 *Validation study*

Psychological reactance represents a clinically useful construct which may help to understand patients' health behaviors and treatment adherence. Indeed, health professionals' persuasive attempts to convince patients to follow the prescribed treatment are not always succeeding.

The aim of this validation study was to identify the factorial structure of the Hong Psychological Reactance Scale in a general population sample, to better understand the nature of psychological reactance (Brehm, 1966, 1972; Brehm & Brehm, 1981) and to provide additional data to factor analyses previously carried out (Brown et al., 2011; De las Cuevas et al., 2014b; Hong, 1992; Hong & Faedda, 1996; Hong & Page, 1989).

The exploratory factor analyses yielded a 4-factor structure, supporting neither the unidimensionality of the scale nor previous models (Brown et al., 2011; De las Cuevas et al., 2014b; Hong, 1992; Hong & Faedda, 1996; Hong & Page, 1989).

Although the number of factors is in line with HPRS structures found in previous validation studies (Brown et al., 2011; Hong, 1992; Hong & Faedda, 1996; Hong & Page, 1989), items loading to each factor are different. Further, as expected, psychological reactance was found to be positively correlated with both mental pain and psychological distress, indicating the more a person is distressed or shows mental pain, the more is likely to be reactant to external influences. According to De las Cuevas and colleagues (2014), psychological reactance may have a role in individuals' beliefs regarding their health status. The Authors (De las Cuevas et al., 2014) suggest that the more individuals show high levels of psychological reactance the less are likely to believe or follow medical advices.

An inverse correlation between psychological reactance and both euthymia and well-being was also detected. These findings confirm those reported by Lara-Cabrera and colleagues (2020), pointing out the role of psychological reactance on individual psychological well-being.

### 3.7 Limitations of the studies

As to the cross-sectional and longitudinal studies, despite we calculated the sample size needed using the GPower software (G*Power version 3.1.9.4, Germany), a larger sample may be more representative and should be considered in future studies.

Another limitation is related to the age of participants. We included hypertensive patients from 18 to 70 years of age due to possible high rates of comorbidities and medical complications often reported among older patients. Further, due to the pandemic and related preventive measures, some clinical and psychosocial data were collected through videocalls or by phone and this may have negatively affected the assessment phase. In addition, information about lifestyle habits were collected administering self-report questionnaires leading to possible bias. Finally, particularly in the longitudinal study, several physiological and cardiac parameters were not available from medical records and were not included in statistical analyses.

The preliminary results of the Hong Psychological Reactance Scale validation study should be considered with caution. Main limitations are the exploratory nature of analyses and some low internal consistency values. A subsequent confirmatory factor analysis, considering a larger general population sample, should be performed in order to confirm the 4-factor structure of the Italian version of the Hong Psychological Reactance Scale found in our study.

## 3.8 Clinical implications and conclusions

As to the cross-sectional study, findings highlight the relevance of psychosocial factors and psychosomatic syndromes, particularly allostatic overload and illness denial, in understanding the clinical course and prognosis of hypertension, as well as differences in psychological variables among patients with essential hypertension compared to normotensive controls.

Further, the longitudinal study confirms the temporal stability of several psychosomatic syndromes and pointed out changes in stress and mental pain as well as in psychological well-being and quality of life rates at one-year follow-up, suggesting on one hand the possible beneficial role of adherence to both pharmacological and non-pharmacological treatments and on the other hand the impact of COVID-19 outbreak on quality of life in hypertensive patients.

Regardless findings should be considered with caution due to the limitations previously reported, one of the major strengths of both cross-sectional and longitudinal studies lies in the use of a clinimetric approach for the assessment of several psychosocial variables. Clinimetrics, defined as the science of clinical measurements (Fava et al., 2012; Feinstein, 1982), through sensitive scales, allows to detect psychological symptoms, psychological well-being and related clinically significant changes over time as well as subthreshold symptoms among different clinical and non-clinical populations.

To the best of our knowledge, the HPRS validation study represents the first attempt to validate the Italian version of the Hong Psychological Reactance Scale. Although a confirmatory factor analysis should be carried out to confirm our results, the factorial structure found is in line with findings from previous validation studies. The utility of this self-report instrument lies in its feasible and rapid administration. Further, it may also be particularly useful in order to understand the role of psychological reactance in both clinical and non-clinical populations.

Overall, these studies provide new insights into the clinical relevance of psychosocial factors and psychosomatic syndromes in the field of cardiovascular health, with several important clinical implications for its pharmacological and non-pharmacological management.

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