

## ORIGINAL PAPER

# Sex differences in adherence to antihypertensive treatment in patients aged above 55: The French League Against Hypertension Survey (FLAHS)

Mathilde Lefort MSc<sup>1</sup> | Lola Neufcourt MSc<sup>1</sup>  | Bruno Pannier MD<sup>2</sup> | Bernard Vaisse MD<sup>2,3</sup> | Sahar Bayat MD, PhD<sup>1</sup> | Olivier Grimaud MD, PhD<sup>1</sup> | Xavier Girerd MD, PhD<sup>2,4</sup>

<sup>1</sup>Univ Rennes, EHESP, REPERES (Recherche en Pharmaco-épidémiologie et Recours aux Soins) – EA 7449, Rennes, France

<sup>2</sup>Comité Français de Lutte Contre l'Hypertension Artérielle (CFLHTA), Paris, France

<sup>3</sup>Service de Cardiologie: Rythmologie et HTA, Marseille Cedex, France

<sup>4</sup>Sorbonne Université, Assistance Publique des Hôpitaux de Paris, Unité de Prévention Cardio- Vasculaire. Hôpital de La Pitié-Salpêtrière, Paris Cedex, France

## Correspondence

Lola Neufcourt, MSc, Univ Rennes, EHESP, REPERES (Recherche en Pharmaco-épidémiologie et Recours aux Soins) – EA 7449, Rennes, France.  
Email: lola.neufcourt@ehesp.fr

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Despite the availability of efficient therapies to reduce the risk of cardiovascular complications, poor adherence to antihypertensive (anti-HTN) drugs is frequent, especially during the first year of treatment and among uncontrolled/resistant hypertensive patients. The aim of the study was to identify factors associated with adherence to anti-HTN treatment and to examine whether they differ across sex. A total of 2743 treated hypertensive participants to the cross-sectional Metascope survey (France, 2015) aged 55 years or more were included. The authors measured adherence to anti-HTN treatment using the 6-item Girerd compliance test. Variations in adherence were examined using the Rao-Scott statistics and Poisson regression. Overall, 63.6% of participants were adherent to anti-HTN treatment. Adherence was more frequent among women than men (69% vs 58%,  $P < 10^{-4}$ ). For both sexes, level of adherence was positively associated with age ( $P < 10^{-4}$ ), but inversely associated with number of anti-HTN tablets, number of tablets taken for metabolic diseases, history of cardiovascular diseases, number of other chronic diseases (all  $P < 10^{-4}$ ). The inverse relationship between adherence and the number of anti-HTN tablets significantly differed between sexes ( $P < 10^{-4}$ ): Adherence decreased sharply when taking two or more anti-HTN tablets in men, whereas the decrease in women was only observed when taking three or more anti-HTN tablets. This study suggests that adherence to anti-HTN treatment is higher among women, decreases with the number of tablets prescribed, and differentially so across sex. Reducing the number of tablets for anti-HTN treatment may improve adherence, especially among men and patients with multiple comorbidities.

## 1 | INTRODUCTION

Despite the effectiveness of antihypertensive (anti-HTN) therapies, the proportion of patients regularly taking their medication is low, even in the context of secondary prevention.<sup>1</sup> It is estimated that about half of the patients being prescribed anti-HTN drugs stop taking treatment within the first year.<sup>2</sup> A similar level of adherence is

observed among patients with uncontrolled and/or resistant hypertension.<sup>3</sup> This is likely to result in significant clinical<sup>4,5</sup> and economical costs. An economic evaluation suggested that €332 million could be saved in five European countries over a 10-year period if compliance with anti-HTN treatment rose from 49% to 70%.<sup>6</sup> Understanding the determinants of nonadherence to anti-HTN is thus of major importance from a clinical but also a public health point of view.

Lefort and Neufcourt contribute equally.

Adherence to treatment is ideally measured using electronic devices monitoring drug intake, combined with measures of drug blood concentrations. The use of validated questionnaire, less costly noninvasive and easily usable in a daily practice, is also common in this area of research.<sup>7</sup> Based on the latter method, studies have shown that age, history of cardiovascular disease (CVD), and social status were positively associated with adherence.<sup>8,9</sup> Whether sex determines adherence is less clear. A study of 484 treated hypertensive patients using the “6-item Girerd compliance test” showed similar levels of adherence to anti-HTN medication in men and women,<sup>8</sup> whereas another study using the same questionnaire found a better adherence in women.<sup>9</sup> Also, some studies have looked at the association between adherence and the number of tablets. This is important since anti-HTN drugs may be prescribed individually (free-drug combination) or in association as fixed-dose combination (two drugs in the same tablet). In a European study, each increase in the number of anti-HTN medications led to 85% and 77% increase in nonadherence ( $P < 0.001$ ) in the UK and Czech populations, respectively. Other factors affecting adherence were age, sex, and class of prescribed antihypertensive drugs.<sup>10</sup> Similarly, in a study involving 873 general practitioners' attendants in France, the number of tablets was associated with nonadherence among men only, whereas adherence decreased with increasing number of types of drugs among women.<sup>9</sup>

In this context, the objectives of our study were first to identify the factors associated with adherence to anti-HTN treatment and second to examine whether these factors differed across sex.

## 2 | METHODS

### 2.1 | Study population

Data are from the Metascope cross-sectional survey (TNS Healthcare, France). This is based on a panel of 20 000 households, recruited by quota sampling in order to ensure representativeness to the French population.<sup>11</sup> Information was collected by self-administered questionnaires sent by post between June 01, 2015, and July 31, 2015. We included respondents aged 55 years or more (they represent 80% of the treated hypertensive patients in France), who declared being treated for hypertension and who answered the adherence questionnaire.

### 2.2 | Evaluation of adherence

The 6-item Girerd compliance test developed by Girerd et al<sup>12</sup> was used to measure adherence with anti-HTN treatment. This test consists of the six yes/no questions enquiring about treatment uptake, shortage, omission, and side effects (please see the Online Supplement S1 for original and translated questions). The 6-item Girerd compliance test has been validated using comparisons with cardiologist assessment of adherence<sup>12</sup> and using a medication event

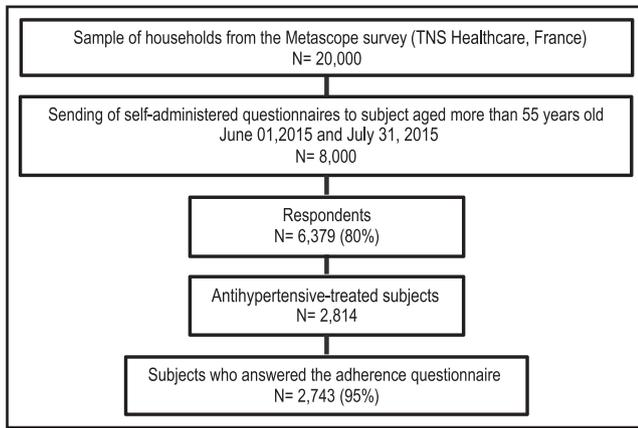
monitoring system.<sup>13</sup> The test classifies participants as adherent if they answered “no” to all questions and as nonadherent otherwise.

### 2.3 | Explanatory variables

The questionnaire enquired about demographic characteristics, anti-HTN treatment, history of CVD (coronary heart diseases, angina pectoris, peripheral artery disease, and stroke) and of other chronic diseases (arthritis, bronchitis, cancer, depression, visual deficiency). To describe their anti-HTN regimen, participants choose from a comprehensive list of drugs. We used these answers to determine the number of anti-HTN tablets taken. A fixed-dose combination was counted as one tablet. Answers regarding treatment of diabetes and/or of hypercholesterolemia were used to derive the number of tablets (0, 1, or 2) taken for other metabolic diseases. Answers from questions about contacts with general practitioners (GP) and cardiologists in the last year were combined to derive three categories: high ( $\geq 3$  visits to GP and  $>1$  to cardiologist), low ( $<3$  to GP, none to cardiologist), or moderate (all others), level of contact with health care. Patients' financial contribution to the therapy costs was identified with a variable labeled copayment. Most people in France do not pay for care at the point of delivery thanks to a supplementary insurance (“assurance complémentaire”) or to the “affection longue durée” scheme for serious diseases. Those were thus classified as “no” for the variable copayment, whereas the minority patients who have to pay upfront for some health care costs were classified as “yes.”

### 2.4 | Statistical analysis

We first described subjects' characteristics in the whole sample and among the adherent group, and we replicated this description for each sex. Because all members of the panel did not provide an answer for this survey, we calculated percentages and performed analyses using a weighting factor correcting for nonparticipation and thus maintaining representativeness of the results. We used the Rao-Scott statistics, which is appropriate for weighted data, to test for statistically significant variations in sex or in adherence.<sup>14</sup> In order to identify differences between sexes, we plotted percentages of adherence in each of three age groups (55 to 64, 65 to 79, 80 or more) according to the number of anti-HTN tablets, separately in men and women. We used Poisson regression to estimate associations between adherence and the number of anti-HTN tablets as well as with other characteristics. Since there was evidence of statistical interaction with sex in the relationship between adherence and the number of anti-HTN tablets and between adherence and age, we fitted regression models separately in men and women. We fitted univariate models and then multivariate models using a stepwise forward selection process with a  $P$ -value threshold of 5%. The analysis was performed on complete cases only. Results are reported as risk ratios (RR) with 95% confidence intervals (CI). In the context of this cross-sectional study, RR corresponds to prevalence ratio. Statistical analyses were performed with the software R version 3.1.0.



**FIGURE 1** Flowchart of the study population

### 3 | RESULTS

Out of 8000 panel members aged 55 years or older, 6379 returned the questionnaire (response rate: 80%). Among respondents, 2814 (44%) were treated for hypertension. Among those, 2743 (95%) answered to the adherence questionnaire and were therefore included in our study (Figure 1).

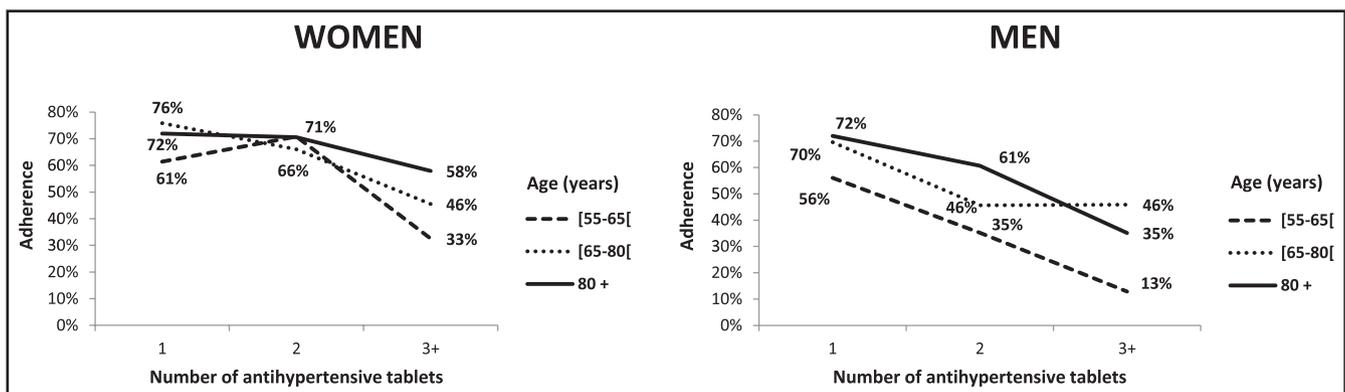
All percentages presented in the following paragraphs, the tables, and in Figure 2 are weighted to ensure representativeness. Table 1 presents the characteristics of the 2743 patients included in the study. Women represented 51.6% of the total respondents. Around 50% of the patients were 65 to 79 years old. Answers about the number of tablets were missing for 285 patients (10%). The latter did not differ with the rest of the sample with respect to sex and age, but they were more adherent (72% vs 63%,  $P = 0.002$ , data not shown). Most patients took one anti-HTN tablet (58.2% vs 31.6% taking two tablets or more). More than a half of the sample (53.9%) also took one tablet or more for metabolic diseases simultaneously with their anti-HTN treatment. About one in four (23.8%) participants declared a history of CVD, but more than two-thirds presented one or more other chronic diseases (68.3%). The majority of participants had regular contacts with GPs and/or cardiologists (intermediate and high contact with health care: 82.7%) and were exempted from copayment (76.3%). Sexes differed with respect to

the proportions taking one anti-HTN tablet (61.3% of women vs 54.9% of men), the proportions reporting a history of CVD (16.8% vs 31.2%) and that of reporting at least two other chronic diseases (26.6% vs 16.3%).

Overall, 62.4% of the participants were adherent to anti-HTN treatment (Table 2). Level of adherence was positively associated with age ( $P < 10^{-4}$ ), but inversely associated with the number of anti-HTN tablets, number of tablets taken for metabolic diseases, history of CVD, number of other chronic diseases, level of contact with health care (all  $P < 10^{-4}$ ). Copayment was associated with higher adherence (71.0% vs 59.9%,  $P < 10^{-4}$ ).

Adherence was higher among women (68.1% vs 56.4%,  $P < 10^{-4}$ ). The inverse associations previously reported in the whole sample between adherence and age, number of anti-HTN tablets, number of tablets taken for metabolic diseases, history of CVD, number of other chronic diseases, level of contact with health care were statistically significant for both sexes. However, the inverse association between adherence and the number of anti-HTN tablets differed between men and women. As illustrated in Figure 2, adherence in men decreased sharply and gradually as the number of tablets anti-HTN increased, with an exception of the change from 2 to 3 or more tablets in the 65-80 years age group. Tests for linear trends in all the three age groups for men were all statistically significant (all  $P < 10^{-4}$ ). In women, adherence remained at a high level when taking one or two tablets and decreased only among those taking three or more anti-HTN tablets. Linear trend was statistically significant only in the 65- to 80-year age group. This sex difference regarding the relationship between adherence and the number of anti-HTN tablets was statistically significant (test for interaction  $P < 10^{-4}$ ).

The inverse relationship between the number of anti-HTN tablets and adherence was confirmed in multivariate analysis with specific patterns for each sex (Table 3). Adherence dipped by nearly 30% among women taking three or more anti-HTN tablets ( $RR_{3+ \text{ vs } 1} = 0.72$ , 95% CI = [0.58; 0.90]), whereas it gradually decreased with increasing number of tablets among men ( $RR_{2 \text{ vs } 1} = 0.74$ , 95% CI = [0.65; 0.85];  $RR_{3+ \text{ vs } 1} = 0.57$ , 95% CI = [0.45; 0.72]). The pattern of decreasing adherence to anti-HTN treatment when taking two or more tablets for other metabolic diseases was also confirmed. Age, history of CVD, and number of other chronic



**FIGURE 2** Evolution of adherence according to the number of antihypertensive tablets by age stratified on sex. A, Women. B, Men

**TABLE 1** Distribution of patients' characteristics

	Whole sample (N = 2743)		Women (N = 1424)		Men (N = 1319)		p <sup>b</sup>
	N	% <sup>a</sup>	N	% <sup>a</sup>	N	% <sup>a</sup>	
Sex							
Women	1424	51.6					
Men	1319	48.4					
Age							
55-65	720	32.4	366	31.7	354	33.1	0.547
65-80	1545	49.6	802	49.5	743	49.7	
80+	478	18.0	256	18.8	222	17.2	
Number of anti-HTN tablets							
1	1600	58.2	879	61.3	721	54.9	0.001
2	629	23.4	291	21.1	338	25.9	
3+	229	8.2	102	7.0	127	9.4	
NA	285	10.2	152	10.6	133	9.8	
Number of tablets taken for metabolic diseases							
0	1278	46.1	731	50.7	547	41.1	<10 <sup>-4</sup>
1	1116	41.1	549	39.1	567	43.3	
2	349	12.8	144	10.2	205	15.6	
History of cardiovascular diseases							
No	2091	76.2	1184	83.2	907	68.8	<10 <sup>-4</sup>
Yes	652	23.8	240	16.8	412	31.2	
Number of other chronic diseases							
0	872	31.7	367	25.6	505	38.1	<10 <sup>-4</sup>
1	1284	46.7	683	47.8	601	45.6	
2+	587	21.6	374	26.6	213	16.3	
Contact with health care							
Low	381	14.0	207	14.7	174	13.3	<10 <sup>-4</sup>
Intermediate	1284	46.8	730	50.8	554	42.5	
High	992	35.9	443	31.3	549	40.6	
NA	86	3.3	44	3.1	42	3.5	
Copayment							
Yes	636	23.1	394	27.7	242	18.2	<10 <sup>-4</sup>
No	2091	76.3	1021	71.7	1070	81.2	
NA	16	0.6	9	0.6	7	0.6	

Anti-HTN, antihypertensive.

<sup>a</sup>Weighted percentages<sup>b</sup>P comparing women to men, complete case analyses

diseases remained independently associated with adherence after full-adjustment, but this was no longer observed for the parameters level of contact with health care and copayment.

## 4 | DISCUSSION

We aimed to identify determinants of adherence to anti-HTN treatments in a representative sample of the French population aged more than 55 and to study these determinants across sexes.

Our results suggest that adherence increases with age, is higher among women, and decreases with the number of anti-HTN tablets. An original finding is the sex difference in the threshold of the number of anti-HTN tablets when adherence drops. Specifically, adherence decreased gradually for each additional tablet in men, whereas in women, adherence only dropped when taking three or more tablets.

Other studies have shown poorer adherence to anti-HTN treatment in younger patients.<sup>8,15,16</sup> One explanation could be that older people tend to be more aware, more interested in health issues,

**TABLE 2** Rate of adherence in men and women

	Whole sample		Sex			
			Women		Men	
	Adherence (% <sup>b</sup> )	P <sup>c</sup>	Adherence (% <sup>b</sup> )	P <sup>c</sup>	Adherence (% <sup>b</sup> )	P <sup>c</sup>
Complete case sample (N <sup>a</sup> = 2370)						
N <sup>a</sup> (% <sup>b</sup> )	1480 (62.4)		835 (68.1)		645 (56.4)	
Age						
55-65	55.3	<10 <sup>-4</sup>	62.4	0.020	47.9	0.001
65-80	65.9		71.2		60.3	
80+	65.6		69.7		62.9	
Number of anti-HTN tablets						
1	68.0	<10 <sup>-4</sup>	70.3	<10 <sup>-4</sup>	65.2	<10 <sup>-4</sup>
2	56.0		68.5		45.0	
3+	41.6		47.1		37.4	
Number of tablets taken for metabolic diseases						
0	68.9	<10 <sup>-4</sup>	72.8	<10 <sup>-4</sup>	63.7	<10 <sup>-4</sup>
1	61.2		66.5		56.3	
2	43.8		51.0		39.0	
History of cardiovascular diseases						
No	66.8	<10 <sup>-4</sup>	70.9	<10 <sup>-4</sup>	61.3	<10 <sup>-4</sup>
Yes	49.9		54.9		47.0	
Number of other chronic diseases						
0	66.5	<10 <sup>-4</sup>	74.8	<10 <sup>-4</sup>	60.4	0.004
1	64.1		70.4		57.2	
2+	53.2		57.6		45.6	
Contact with health care						
Low	70.9	<10 <sup>-4</sup>	77.9	0.0004	62.1	0.010
Intermediate	65.4		69.6		60.1	
High	55.6		61.3		51.1	
Copayment						
Yes	71.0	<10 <sup>-4</sup>	73.2	0.023	67.1	0.002
No	59.9		66.1		54.2	

Anti-HTN, antihypertensive.

<sup>a</sup>Complete cases only<sup>b</sup>Weighted percentages<sup>c</sup>P comparing adherence to nonadherence

and perceive hypertension as a higher risk than younger people do. Consequently, they might comply with a refill schedule for their anti-HTN treatments—the first step of a better adherence—at higher rates compared with a younger group and might also pay more attention to correctly take it.<sup>17,18</sup> Higher adherence in the older population may also be explained by a closer proximity with health care providers, which is the case for those residing in health care setting or in nursing homes.<sup>19</sup>

The relationship between sex and adherence is more controversial because of inconsistent conclusions between studies, as shown in the review from Jin et al.<sup>19</sup> In this review, eleven out of twenty-two

studies suggested that female patients are more likely to have better adherence, four reported the inverse relationship, and seven found no association.<sup>19</sup> In a more recent study, male sex was found to be a significant predictor of nonadherence (adjusted OR = 1.12 [95% CI 1.07-1.17],  $P < 0.05$ ).<sup>15</sup>

Several studies reported a significant inverse association between adherence and the number of anti-HTN tablets.<sup>8,9,17,20,21</sup> In particular, in a review published in 2005, adherence did not seem to correlate with the number of drugs prescribed but decreased with the number of daily takes.<sup>22</sup> The suggested “fixed-dose” combinations could be more convenient and simpler to use than a free-drug

**TABLE 3** Association between adherence and patients' characteristics by sex (Poisson regression stratified on sex)

	Women (N = 1227)		Men (N = 1143)	
	Bivariate analysis	Multivariate analysis	Bivariate analysis	Multivariate analysis
Whole sample (N = 2370)	RR [95% CI]	RR [95% CI]	RR [95% CI]	RR [95% CI]
Age				
55; 65	1.00	1.00	1.00	1.00
65; 80	1.14 [1.03-1.26]	1.15 [1.05-1.28]	1.26 [1.1-1.45]	1.32 [1.15-1.5]
80+	1.12 [0.99-1.27]	1.19 [1.05-1.35]	1.27 [1.07-1.5]	1.45 [1.23-1.7]
Number of anti-HTN tablets				
1	1.00	1.00	1.00	1.00
2	0.97 [0.89-1.07]	1.01 [0.92-1.11]	0.69 [0.6-0.79]	0.74 [0.65-0.85]
3+	0.67 [0.54-0.84]	0.72 [0.58-0.9]	0.57 [0.45-0.73]	0.57 [0.45-0.72]
Number of tablets taken for metabolic diseases				
0	1.00	1.00	1.00	1.00
1	0.91 [0.84-0.99]	0.94 [0.86-1.02]	0.88 [0.79-0.99]	0.92 [0.83-1.03]
2	0.70 [0.58-0.84]	0.74 [0.61-0.88]	0.61 [0.5-0.75]	0.67 [0.55-0.81]
History of cardiovascular diseases				
No	1.00	1.00	1.00	1.00
Yes	0.77 [0.68-0.88]	0.80 [0.7-0.91]	0.77 [0.68-0.87]	0.84 [0.74-0.96]
Number of other chronic diseases				
0	1.00	1.00	1.00	1.00
1	0.94 [0.86-1.03]	0.92 [0.85-1.01]	0.95 [0.85-1.06]	0.94 [0.85-1.05]
2+	0.77 [0.68-0.87]	0.78 [0.7-0.88]	0.76 [0.63-0.91]	0.74 [0.62-0.88]
Contact with health care				
Low	1.00	Not included in the multivariate model	1.00	Not included in the multivariate model
Intermediate	0.89 [0.81-0.98]		0.97 [0.83-1.13]	
High	0.79 [0.70-0.88]		0.82 [0.7-0.97]	
Copayment				
Yes	1.00	Not included in the multivariate model	1.00	Not included in the multivariate model
No	0.90 [0.83-0.98]		0.81 [0.72-0.91]	

Anti-HTN, antihypertensive.

combination and therefore achieve better adherence.<sup>23</sup> Contrary to this body of evidence, several studies argue for an opposite relationship. For instance, Lagi et al reported that adherence increased with the number of anti-HTN tablets, from 47% with a one-drug treatment to 66% with a three-drug treatment.<sup>24</sup> However, this study suffers from poor statistical power and from a lack of adjustments on important confounding factors. Adherence was also high with high number of pills in two further studies<sup>18,25</sup> but the recruitment of newly treated patients might explain their finding, as treatment duration negatively affects adherence.<sup>26</sup> Finally in a recent study, the number of anti-HTN drug classes taken once or more by the participants was positively associated with adherence ( $P < 0.0001$ ).<sup>15</sup> However, adherence rate was low in this study (39.4% among hypertensive patients) which could explain this finding.

To our knowledge, our study is the first to explore specifically sex differences in the relationship between adherence and number of tablets.

Our original finding is the differing thresholds of number of anti-HTN tablets at which adherence drops in men and women. Specifically, adherence decreased sharply when taking two or more antihypertensive tablets in men, whereas the decrease in women was only observed when taking three or more antihypertensive tablets. The fact that, compared to men, women remain adherent when taking two anti-HTN tablets is consistent with what is known regarding health behavior and health care seeking in this sex. Women have higher level of care seeking than men. They more often refer themselves to the GP and more often for issues related to prevention.<sup>27</sup> In Canada, women reported that they would visit a family physician in response to both physical and mental health concerns to a greater extent than did men.<sup>28</sup> This attitude of feeling more concerned and getting involved in the therapeutic process in agreement with the recommendations seems to be more developed among women and could partly explain their suggested better adherence compared to men. This sex difference may partly explain why French

women present higher rate of controlled hypertension (66.5% of hypertensive women vs 44.9% of hypertensive men),<sup>29</sup> as well as a much lower frequency of hypertension-related cardiovascular events (36.4/100 000 strokes in women aged less than 65 years vs 66.0/100 000 strokes in men in 2014).<sup>30</sup> There may be a need for health care professionals to pay particular attention to the initiation of anti-HTN treatment comprising more than one daily take in men.

Our results suggest that histories of cardiovascular diseases (CVD) and of other chronic diseases are inversely associated with adherence in both sexes. Similar to the association with anti-HTN tablets, we found that adherence decreased with increasing number of tablets taken for other metabolic problems, although there were no differing patterns between sexes for this parameter. Conversely, the number of concurrent medications was reported to be positively associated with adherence in another study.<sup>25</sup> However, our results are consistent with those from ODACE where the number of tablets or treatments other than the anti-HTN ones was associated with poorer adherence.<sup>9</sup> An interpretation of these findings is that adherence to anti-HTN treatments, and probably to other treatments, depends on the overall number of tablets prescribed to each patient. This point has important implications for the elderly patients who often present comorbidities and are consequently exposed to multiple treatments. Estimations from a nationally representative sample of community-dwelling older adults 62 to 85 years old in United States suggest that 87% of patients used at least one prescription medication and 36% regularly used five or more prescription medications at the same time.<sup>31</sup> The same study showed that in 2010-2011, 15% of older adults were at risk for a potential important drug interaction.<sup>31</sup>

From our findings, it is unclear whether regular contacts with health care or absence of copayment could improve adherence since, after adjustment, there were no associations between these two parameters and adherence in our sample. One possible explanation is that people with higher contact and poorer adherence, as observed in bivariate analyses (Table 3), are probably those with comorbidities and other treatments. A similar explanation could apply to the absence of association between copayment and adherence after adjustment. A related question that we could not explore with our data is whether home support, formal (carer) or informal (family or relative), influences adherence for older impaired patients. Further work based on prospective design would help elucidate these questions.

Results of our study should be interpreted as those from a cross-sectional study with self-declared adherence which despite limitations is often used in this field of research.<sup>7</sup> We also relied on self-reporting which has proved valid tools for ascertainment of CVD history and medication regimen in epidemiological investigations.<sup>32,33</sup> A strength of our study is that it is based on a representative sample of the French population aged more than 55. We were also able to examine the level of adherence with respect to demographic variables and several clinical characteristics such as history of other cardiovascular or chronic diseases. Comparison of adherence studies' results is complex due to the variety of ascertainment methods. Thus, our use of the 6-item Girerd compliance test might hamper comparisons of absolute values of adherence with that of

other studies. However, our finding of sex differences in adherence is based on relative comparison. It would be useful to check whether similar results apply when using other adherence measurement methods. Finally, our study does not allow to explore causes of non-adherence which may be linked to specific anti-HTN drug regimens and interactions between drugs. More detailed information on medications would be necessary in order to investigate such questions.

## 5 | PERSPECTIVES

This study indicates that adherence to anti-HTN treatment varies across sex both in terms of absolute level and in terms of its relationship with the number of tablets in a sample of older adults. An implication of our results is that reducing the number of anti-HTN tablets may improve the level of adherence, particularly in men and in patients with multiple comorbidities. Further research should confirm our results using other adherence measurement tools, explore whether our findings apply to other age groups or other populations, and investigate the effect of a switch from a two-drug treatment to a fixed-dose combination on adherence. Given the likely growth of the absolute number of hypertensive patients and the consequences of nonadherence, this question should receive sufficient attention.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

M. Lefort, L. Neufcourt, O. Grimaud, and X. Girerd formulated the research question. X. Girerd, B. Pannier, B. Vaïsse, and S. Bayat contributed to the study design and analysis plan. M. Lefort performed the statistical analyses. M. Lefort and L. Neufcourt wrote the paper. All authors reviewed and approved the final version.

## ORCID

Lola Neufcourt  <http://orcid.org/0000-0001-6429-0551>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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