# Hyperuricemia, cardiovascular profile, and comorbidity in older men and women: the Pro.V.A. Study

(Running title: Hyperuricemia and comorbidity in the elderly)

Estella MUSACCHIO[a], Egle PERISSINOTTO[b], Leonardo SARTORI[a], Nicola VERONESE[c], Leonardo PUNZI[d], Sabina ZAMBON[a], Enzo MANZATO[c,e] Giovannella BAGGIO[f], Maria-Chiara CORTI[g], Gaetano CREPALDI[e], Roberta RAMONDA[d]

[a] Department of Medicine DIMED - Clinica Medica 1- University of Padova, Padova, Italy

[b]Department of Cardiologic, Thoracic and Vascular Sciences - Unit of Biostatistics, Epidemiology and Public Health - University of Padova, Padova, Italy

[c]Department of Medicine DIMED - Geriatric Unit - University of Padova, Padova, Italy

[d] Department of Medicine DIMED - Rheumatology Unit - University of Padova, Padova, Italy

[e] National Research Council, Aging Branch, Institute of Neuroscience, Padova, Italy

[f] Department of Molecular Medicine DMM, University of Padova, Padova, Italy

[g] Department of Public Health, Regione Veneto, Venezia, Italy

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Address for correspondence and reprints
Roberta Ramonda MD, PhD
Rheumatology Unit
Department of Medicine DIMED
Via Giustiniani 2
35128 Padova, Italy
Ph +39049 8212199
Fax +39049 8212191
roberta.ramonda@unipd.it

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**Abstract**

**Objectives.** Hyperuricemia (HU) is growing worldwide and associated with several medical conditions in the elderly. However, data about older people and possible gender differences are sparse. The aim of this study was to compare HU prevalence rates and association with relevant medical disorders in elderly subjects of both sexes.

**Methods:** Pro.V.A. is a survey of 3099 individuals aged 65+, focusing on chronic diseases and disability. Uric acid (UA) levels were dichotomized using 6.0 mg/dl (females) and 7.0 mg/dl (males), and multivariate logistic regression models were used to estimate odds ratios (ORs) between HU and single comorbidity.

**Results.** HU prevalence was 21.5% in females and 15.8% in males. HU was associated with most anthropometric and laboratory variables in women, but not in men. After adjustment for age, body mass index and renal function, HU was independently associated with the presence of cardiovascular diseases in both sexes. In women, HU was associated with hand osteoarthritis (OR=1.52; 95%CI: 1.12-2.08) and edentulism (OR=1.31; 95%CI: 1.01-1.71), while resulted protective for osteoporosis (OR 0.69; 95% CI: 0.53-0.91). In men, HU was significantly related with knee osteoarthritis (OR=1.72; 95%CI: 1.06-2.79) and chronic obstructive pulmonary disease (OR=1.60; 95%CI: 1.04-2.45). The presence of ≥4 comorbidities was a stronger determinant of HU in men (OR=2.54; 95%CI: 1.21 – 5.37) than in women (ns).

**Conclusions.** Patterns of age-dependent UA increase are markedly different in men and women. HU prevalence is substantial and its association with other diseases is gender-specific connoting a peculiar clinical profile.

## Introduction

Uric acid (UA) is the final product of purine metabolism. Mild to moderate hyperuricemia (HU) is relatively common, and related to a variety of modifiable environmental factors (lifestyle, nutrition, comorbidities and therapies) and non-modifiable factors such as gender, age, and genetics, while highest levels may be found in conditions characterized by increased catabolism (1-2). HU and consequent microcrystal deposition are associated with gout as well as with chronic heart and/or renal failure (3-5). The prevalence of HU has been growing worldwide for several decades. Many reports document an independent association of HU with cardiovascular (6-8) and metabolic diseases (9-12). Moreover, studies carried out in the last decade demonstrated the relevance of HU as a risk factor for the outcome of concomitant diseases (13-15). On the other hand, UA plays a role as endogenous antioxidant, being responsible for most of the antioxidant capacity in human plasma (16).

Different thresholds, ranging from 5.2 mg/dl to 7.7 mg/dl, have been applied to define HU in the epidemiological literature. Furthermore, taking into account both the physiological changes of aging and the differences between the genders, age-specific and sex-specific cut-offs have been suggested to define warning conditions, with thresholds for women lower than for men (17-21). In adulthood, unhealthy lifestyles and unbalanced diets rise UA levels. Additionally, as people age, impaired renal function, comorbidities, and drug interference with purine metabolism can lead to frank HU. As the elderly population increases and additional complications are associated with HU, the socioeconomic burden stemming from this condition is expected to rise, particularly in places such as Italy where the elderly fraction of the population is large (22,23). Deeper insights are needed to better understand the impact of HU among the elderly, in terms of risks and comorbidities. A gender-specific approach might yield better management of this condition and its consequences.

To contribute to the debate, the present study analyzed a large sample of older Italians to investigate serum UA levels, the prevalence of HU and its gender-specific association with other comorbidities.

## Methods

*Study population*. The Pro.V.A. (Progetto Veneto Anziani) Study is a large observational community-based cohort survey of 3,099 subjects aged 65 and older (mean age 76.8±8.7 yrs) (1245 males and 1854 females, mean age 76.6±8.0 and 76.8±7.9 yrs respectively), all Caucasians residing in the Venetian Region of Northeast Italy. The Pro.V.A. was designed to assess the functional status and the prevalence of disability in a representative sample of the Italian population (24). All of the participants were interviewed at home, then referred to their local hospital for a detailed medical evaluation. Subjects subsequently underwent extensive laboratory assessments that included hip and knee X-rays. Transportation was provided for the disabled and home visits were arranged for homebound individuals. All interviewers, nurses and physicians participating in the study were calibrated and trained on standardized data collection using questionnaires, performance measures, instrumental tests and physical examinations. The study was approved by the local research ethic committees (Rovigo and Padova) and written informed consent was obtained from all participants.

The present work initially included 3,068 subjects for whom complete information was available. Patients taking allopurinol were excluded (n=97) from the analyses, yielding to a final population of 2,971 studied subjects.

*Measurements.* Anthropometric parameters as well as blood pressure values were obtained by trained physicians using standard methods. Participants were considered hypertensive if they had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or were taking antihypertensive medications (7). Body mass index (BMI) was calculated as body

weight (kg) by the square of the subject's height ($m^2$). Blood samples were collected after overnight fasting for biochemical analysis, to determine UA and other parameters, listed in Table 1. To calculate the estimated glomerular filtration rate (eGFR) in milliliters per minute per 1.73$m^2$, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was applied (25).

*Comorbidity, socio-economic status, and lifestyle factors*. The presence of pathological conditions was clinically determined by board-certified physicians who examined all the clinical information collected for each participant in the study and performed a general physical examination with an emphasis on vascular, neurological and rheumatological signs. Disease ascertainment was based on the symptoms, signs, and documentation available at the time of the visit, including previous and actual medical charts and reports from blood tests and X-rays carried out at the study clinic. Moreover, for some conditions, instrumental assessment was also performed (i.e. quantitative ultrasonographic bone mass determination in the case of osteoporosis). Comorbidity was considered with respect to: kidney diseases, cardiovascular disorders (angina, myocardial infarction (AMI), congestive heart failure (CHF), stroke, peripheral arteriopathy (PAD), hypertension), chronic obstructive pulmonary disease (COPD), diabetes, osteoporosis, neoplasms of any kind and stage, Parkinson's disease. Hand, knee, and hip osteoarthritis (OA) as well as the presence of chondrocalcinosis were assessed according to Altman (26). Finally, the ability to perform selected activities of daily living (ADL) was also investigated and the need for help was recorded for rising from bed/chair, transferring, bathing, dressing, and using a toilet. In the present analysis, disability was defined as inability in more than one ADL.

The information used to describe socio-economic and lifestyle factors was self-reported during the baseline interview. For socio-economic status, monthly income was dichotomized at 500 euros and educational level was dichotomized at eight years of school attended

(corresponding to compulsory education). For lifestyle, smoking was assessed by means of seven questions concerning current or past (persisting for at least one year) smoking patterns. With respect to smoking status, subjects were classified as "never," "former" or "current." Based on the home interview, participants were categorized as drinkers if they reported alcoholic beverages (wine, beer, and/or spirits) habitually in the previous month. Heavy alcohol drinkers were defined using the criteria suggested by the National Institute of Alcohol Abuse and Alcoholism, i.e., more than 15 drinks weekly for men and 8 for women (27).

*Statistical analysis*. On the basis of the sex-specific distribution of UA levels, HU was deemed present when values were above 6.0 mg/dl for females and above 7.0 mg/dl for males, as suggested by other studies (28-31). Sex- and age-standardized prevalence were estimated using the direct standardization method performed on the target population structure. If normality, assessed with Shapiro-Wilk test, was satisfied, quantitative variables were summarized as means ± standard deviations, and qualitative ones as frequency distributions. Analysis of variance or t test was used to compare mean values among groups for normally distributed variables, and the non parametric Mann-Whitney test for non-normal variables. Chi square test was applied to compare categorical distributions. Logistic regression analyses were performed in order to estimate the independent contribution (adjusted p, ORs, and 95% CI) of comorbidities to HU -- after adjustment for variables hypothesized to be in the causal pathway (age, BMI, eGFR). Moreover, to assess the role of increasing numbers of concomitant diseases in determining HU, the presence of comorbidities was categorized into three classes (none, 1-3, ≥4), where ≥4 corresponded to the 90th percentile. A p level lower than 0.05 was considered significant. All statistical analyses were performed using SAS Statistical Software Package version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

*UA distribution*. Mean UA levels were higher in men than in women (5.67±1.41 vs. 5.03±1.53 mg/dl, p<0.0001). Distribution analysis by gender also revealed marked differences. Figure 1 reports the prevalence of males and females by UA classes of 1-unit increments and cumulative frequency distribution, while Figure 2A shows UA mean values by age group. The pattern of age-dependent increase in UA concentrations markedly differed in men and women, the latter showing a more linear trend.

*HU prevalence*. HU overall prevalence was 19.2 %, (with women at 21.5% and men at 15.8%, p<0.0001). After adjusting for the sex and age structure of the target population, it was 18.3%, 15.1%, and 20.8% for the population as a whole, males, and females, respectively. When patients were stratified by age groups (Figure 2, panel B), the prevalence of HU varied remarkably and increased with age only in women (p<0.0001) while rates in men were not statistically different in the age groups.

*Association of HU with anthropometric and laboratory findings*. The main population characteristics by uricemic status and gender are shown in Table 1. HU was associated with most conditions in women. In men, statistically significant associations were found only for anthropometric features (weight, BMI, waist circumference), and some bio-humoral parameters (eGFR, vitD, PTH, Ca, triglycerides). Notably, data from males did not show any association between HU and inflammation indexes.

*Lifestyle factors*. Smoking, alcohol drinking, education level, and income were considered to define habits and socio-economical status. Alcohol intake was also considered separately for wine, beer and spirits, and heavy drinkers fraction. No difference was found between HU and controls when the population was analyzed as a whole (data not shown), nor it was when keeping sexes apart. It must be noted that the fraction of current smoking, heavy drinking, and high education was extremely low among females, that could affect the statistical relevance.

*Comorbidity.* The analysis of comorbidities by gender is reported in Table 2. At the univariate analysis (Table 2, left columns), a strong association existed for cardiovascular diseases and HU in both sexes. HU also appeared to play a role in musculoskeletal conditions. In particular, HU was associated with a higher prevalence of knee OA, disability in ≥1 ADL, and edentulism and with a lower prevalence of osteoporosis. For the two latter conditions the association was evident only in women. Conversely, association with other disorders (dyslipidemia and COPD) were found only in men, notwithstanding a higher prevalence of females presenting with a comorbid state for conditions related to metabolic alterations such as, dyslipidemia and diabetes.

To better characterize these associations, logistic regression analyses models were performed, progressively adjusting for more relevant confounding factors, namely age, BMI, and eGFR (Table 2, right columns). In women, HU resulted significantly associated with CVD (particularly with PAD and hypertension). In this gender, among musculo-skeletal and neurological disorders investigated, HU was associated with a reduced presence of osteoporosis (OR=0.69; 95%CI: 0.53-0.91) and higher of hand OA (OR=1.52; 95%CI: 1.12-2.08) and edentulism (OR==1.31; 95%CI: 1.01-1.71), while no significant association emerged between HU and metabolic diseases investigated. In men, on the contrary, HU was significantly associated with most CVD investigated and with knee OA (OR=1.72; 95%CI: 1.06-2.79) and COPD (OR=1.60; 95%CI: 1.04-2.45).

The risk of HU progressively increased the presence of concomitant comorbidities (Table 3), with an association stronger in men than in women (adjusted OR=2.54 vs ns in women).

## Discussion

In this study including a large cohort of men and women older than 65 years, we have shown that HU is a highly prevalent condition affecting about a person in five people. However, important differences between males and females emerged.

In fact, although the UA remains significantly higher for all age-classes in men than in women, the prevalence of HU resulted significantly higher in women than in men. In all the sample, the prevalence of HU in women was 21.5%, while in men was 15.8%. Interestingly, the prevalence of this condition increased of only 6% in men from 65 to over 90 years, but doubled in women (from 15.3% in those having 65 years to 34.4% in the nineties). Therefore, the adoption of sex specific cut-offs seems to be fundamental for better identifying the presence of HU in females, particularly in advanced age. In the search for factors that might explain this, we analyzed several variables that may have gender-associated behavior in older ages, including the multi-task hormone vitamin D, the sex hormone binding globulin (SHBG) - for its role in modulating circulating sex hormones and for recent reports of an association with inflammation indexes and insulin resistance (32), hypertension, GFR, and renal diseases. The pattern most closely matched GFR (data not shown). Likely, more than a single condition contributes to the discrepancy. It must also be taken into account that we analyzed an elderly population, in which all women were postmenopausal. The well-known protective effect of estrogens, which is lacking in older age, may be responsible, at least in part, for such differences as reported by others (33).

Our data seem to be partially similar to those present in the literature about the prevalence of HU, even if the data in those having more than 65 years are very limited. In the NANHES 2007-2008, the overall prevalence of HU (serum urate level >7.0 mg/dl for men and >5.7 mg/dl for women) among U.S. adults was 21.4% (21.1% in men and 21.6% in women), however the mean age of this population was 47 years and 30% were not white (28). A similar figure was evident in China (34). Comparing our findings with those obtained by

Trifirò and colleagues (23) in a nationwide population-based study in Italy in the years 2005-2009, the age-specific HU prevalence rates of our sample are consistent with data referring to 2009 when sex-specific HU cut off were applied. Differences may reflect the data-collecting methodology. In our study, subjects were randomly selected from the local elderly population, whereas the cited reference used longitudinal data including patients' records from general practitioners. However, an American survey found that HU affects about one person out of two over 65 years and more males than females (35). Probably the different dietary patterns between our and this analysis played an important role.

About the association between HU and medical conditions investigated, we found important gender differences and some discrepancies with literature. Consistently, the presence of a higher number of comorbidities was a stronger determinant of HU in men than in women. However, the prevalence of women presenting with a comorbid state was higher than that of men for all conditions related to metabolic disorders, such as obesity, dyslipidemia, inflammation, diabetes, hypertension, thus strengthening the recent finding of an independent predictive role of HU in determining metabolic syndrome in women of the PRO.V.A Study (36). Several cross-sectional and longitudinal studies substantially confirm our results, finding an association between UA and worse metabolic profile stronger in women than in men (37-44). This different association between genders seems to be attributable to several factors, but particularly to the deficiency of estrogens that have uricosuric and metabolic effects (14). Epidemiological and clinical evidence suggests that HU is an independent risk factor for cardiovascular diseases (6,45), being a predictor of incident hypertension in age- and gender-based studies (46). Consistent with these reports, we found a strong association independently of sex between cardiovascular diseases and HU. In men, HU was significantly associated with the presence of COPD. HU seems to be important as early mortality marker in people with COPD and UA seems to inversely associate with respiratory function parameters (47,48).

However, other surveys are needed to understand whether UA could be considered as a risk factor or a consequence of COPD and if lowering UA levels with pharmacological treatment could decrease the onset of the comorbidities associated with HU in our research. Regarding gender differences, HU was associated with a higher presence of disability, also after removing the effect of obesity, age, and renal function in females. This is, to the best of our knowledge, the first research reporting this kind association that further confirms the deleterious effect of HU in women. However, it should be noted that HU reduced the OR of having osteoporosis of about 30%, in agreement with the current literature suggesting that for osteoporosis and fractures HU could be protective (49,50), particularly in women, thanks to its antioxidant properties, that acquire particular relevance when the beneficial effects of estrogen are lacking. Data from men, in the same direction, did not reach significance. Noteworthy, in both sexes the protective action of higher UA levels was evident despite the older age and the worse profile in bone metabolism markers, like the increase in serum parathyroid hormone levels associated with the increase in UA levels. Another cue of a possible protective action of higher UA levels, in agreement with literature reports (51) was found in both sexes for Parkinson's disease but the low prevalence of this condition did not grant enough power to our finding. Preliminary data of the present work, obtained analyzing UA quintiles, indicated that the prevalence of comorbidities increased with increasing UA values, but was lower in Q4 with respect to Q3 for several conditions (i.e. hypertension, CHF, dyslipidemia). This issue deserves few more words. On the one hand it has been hypothesized that the antioxidant properties of UA may be protective against oxidative damage-triggered conditions and related diseases. On the other hand, epidemiological and clinical evidences suggest that HU might be a risk factor for diseases, such as cardiovascular diseases and metabolic syndrome, where enhanced oxidative stress plays an important pathophysiological role. This apparent paradox between protective and toxic effects of UA could be explained by

the observation that higher serum UA levels within normal physiologic levels may have antioxidant effects while abnormally high levels are responsible for oxidative stress (52,53). The controversy relies not only on the apparent paradox between antioxidant and pro-oxidant properties of the molecule but also on the physiological role of oxidative stress (54).

With respect to socioeconomic status and luxury habits, we did not find the association often described by others (2). Possible explanations for this discrepancy lay on the low prevalence of some conditions and on a generalized blunting effect of other more determinant physical and clinical variables in older age. Another odd result is the lack of the association between diabetes and HU in both genders after taking in account possible confounders. However, it is known that patients with recently-diagnosed diabetes tend to have lower SUA levels than non-diabetics (36). Since in the PRO.V.A Study diabetes was diagnosed also through fasting plasma glucose and HbA1c recorded at the same time of the measurement of UA, it is possible that the new cases of diabetes compensate the others, justifying our findings.

We had the opportunity to study a large cohort of elderly subjects and to analyze many variables. As often happens in epidemiological studies, the present work has strengths and limitations; this is a population-based study of a random sample of elderly Italians characterized by a substantial fraction of very old subjects (about 20% over 85 yrs of age), and the results were obtained with standardized protocols that make them suitable for extrapolation to a larger target population. Regrettably, data concerning dietary intake was not recorded, nor was information concerning gout episodes.

An important implication of our findings is that HU is always coupled with comorbidity and altered laboratory findings in the elderly and this association appears to be more frequent in women but more severe in men. Unfortunately, due to the cross-sectional study design it is not possible to define a causative role. Nonetheless, we suggest UA determination that is a rapid and quite inexpensive test as a first line investigation for the presence of medical

disorders in the elderly. In this light, UA lowering could represent another strategy for the treatment of these conditions, particularly CVD. Finally, it is worth noting that the gender differences highlighted here may contribute to a better understanding of the health status of specific older men and women, and warrant more concern for gender-based evaluations and public health measures.

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**Author disclosure statement**

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## Legends to figures

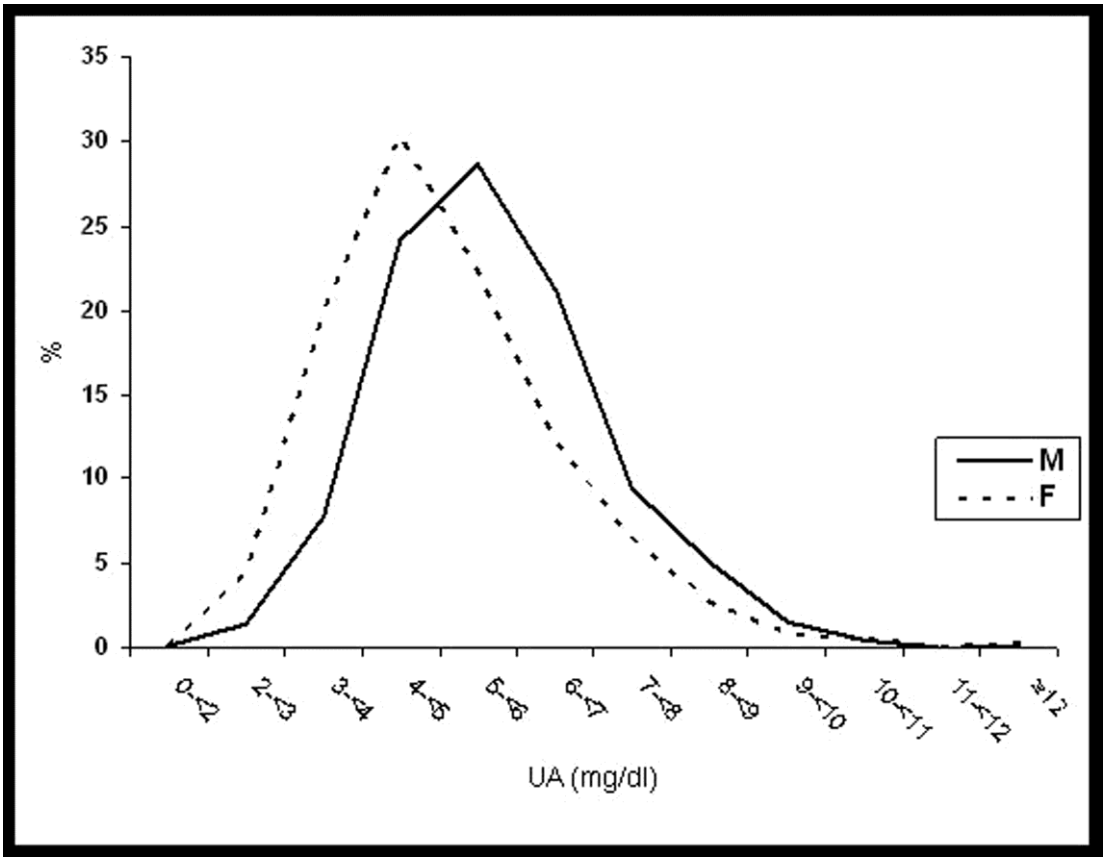


**Figure 1.** Distribution of UA serum levels by sex (1 unit increments from 0 to 12 mg/dl).

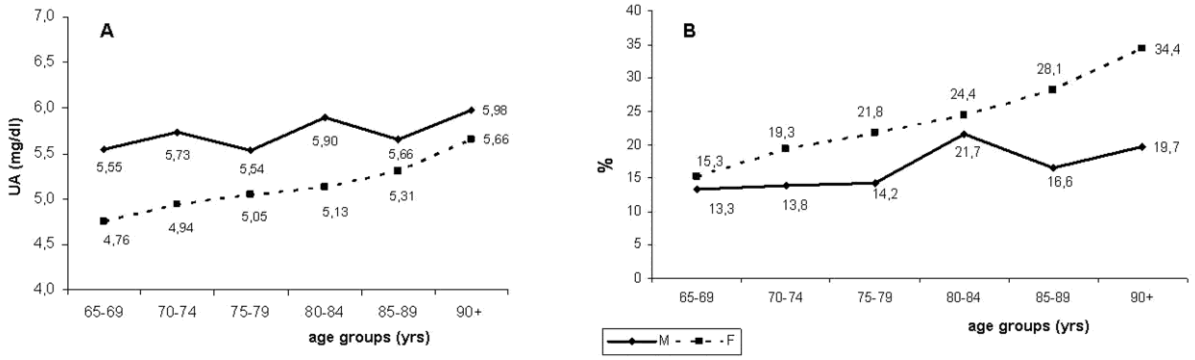


**Figure 2.** UA mean values (panel A) and HU prevalence (panel B) by gender and 5-year age class (F>6.0mg/dl, M>7.0 mg/dl).

**Table 1**. Characteristics of Hyperuricemic (HU) and control (CTR) populations by sex.

| **variable** | **Females (n=1789)** | | | **Males (n=1182)** | | |
|---|---|---|---|---|---|---|
| | **CTR** n=1406 | **HU** n=383 | **p HU vs CTR** | **CTR** n=998 | **HU** n=184 | **Age-adj p HU vs CTR** |
| Age (yrs) | 75.5±7.6 | 78.0±7.9 | <0.0001 | 76.1±78 | 77.3±7.9 | 0.06 |
| Years since menopause (yrs) | 25.7±9.0 | 28.01±9.0 | <0.0001 | - | - | - |
| Uric acid (mg/dl) | 4.41±0.9 | 7.28±1.2 | <0.0001 | 5.24±1.0 | 8.03±0.85 | <0.0001 |
| **Anthropometric** | | | | | | |
| BMI ($kg/m^2$) | 27.5±4.6 | 30.2±5.7 | <0.0001 | 26.5±3.8 | 27.9±3.9 | <0.0001 |
| Waist circumference (cm) | 94.4±12.1 | 101.4±12.3 | <0.0001 | 96.5±9.9 | 101.0±9.9 | <0.0001 |
| **Bio-humoral exams** | | | | | | |
| eGFR (mL/min/1.73mq) | 65.6±14.3 | 53.3±14.9 | <0.0001 | 69.8±14.7 | 58.0±16.4 | <0.0001 |
| VitD (nmol/l) | 64.9±42.0 | 61.2±38.5 | 0.13 | 103.0±64.0 | 92.2±54.0 | 0.04 |
| PTH (ng/l) | 43.2±29.1 | 51.2±37.0 | <0.0001 | 36.3±21.8 | 46.9±24.7 | <0.0001 |
| Ca (mg/dl) | 9.41±0.51 | 9.50±0.51 | 0.004 | 9.36±0.5 | 9.44±0.5 | 0.04 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ESR (mm/h) | 23.6±18.9 | 27.9±18.4 | <0.0001 | 16.3±18.6 | 16.2±14.8 | 0.94 |
| Fibrinogen (mg/dl) | 354.4±84.6 | 367.9±87.1 | 0.007 | 334.7±78.3 | 342.2±84.3 | 0.25 |
| Triglycerides (mg/dl) | 130.7±64.6 | 173.8±109.3 | <0.0001 | 123.3±65.9 | 153.1±81.2 | <0.0001 |
| Total cholesterol (mg/dl) | 237.5±43.0 | 238.7±46.7 | 0.64 | 217.8±43.5 | 221.3±47.9 | 0.33 |
| HDL cholesterol (mg/dl) | 60.0±16.8 | 58.0±19.97 | 0.04 | 56.1±20.4 | 55.1±21.1 | 0.55 |
| Glucose (mg/dl) | 104.9±33.6 | 113.3±38.2 | <0.0001 | 106.7±33.8 | 103.7±21.5 | 0.24 |
| HbA1c (%) | 5.35±1.0 | 5.59±1.1 | 0.0001 | 5.21±1.1 | 5.23±0.9 | 0.79 |
| **Lifestyle & socioeconomic factors** | | | | | | |
| Smoke % | | | | | | |
| No | 88.0 | 84.9 | 0.10 | 23.8 | 23.6 | 0.12 |
| Former | 8.1 | 11.6 | | 59.4 | 65.4 | |
| Current | 3.9 | 3.4 | | 16.8 | 11.0 | |
| Alcohol consumption | 71.8 | 75.5 | 0.15 | 89.8 | 90.7 | 0.69 |
| only beer & spirits | 32.4 | 33.9 | 0.59 | 58.4 | 60.3 | 0.63 |
| heavy drinkers | 1.7 | 1.8 | 0.87 | 26.1 | 29.9 | 0.28 |
| Education (high) % | 4.5 | 2.7 | 0.11 | 7.7 | 6.6 | 0.61 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Monthly income >500 euros | 30.3 | 31.6 | 0.63 | 51.2 | 54.1 | 0.47 |

Hyperuricemia, cardiovascular profile, and comorbidity in older men and women: the Pro.V.A. Study (doi: 10.1089/rej.2016.1834)

**Table 2**. Prevalence and adjusted Odds Ratios and 95% CIs for comorbidities according to different logistic regression analysis models. Role of HU as explanatory variable (Y/N, cut off values: F >6.0mg/dl; M>7.0mg/dl). Covariates* (Age, BMI, eGFR), used as quantitative variables, were sequentially entered from model 1 to model 3.

| **Females** | **CTR** | **HU** | **p** | **Model 1** | **Model 2** | **Model 3** |
|---|---|---|---|---|---|---|
| **Cardio vascular diseases** | | | | | | |
| Any CVD | 54.9 | 76.5 | <0.0001 | **2.53 (1.95-3.29)** | **2.58 (1.95-3.41)** | **2.26 (1.69-3.01)** |
| Angina | 3.2 | 6.0 | 0.01 | **1.81 (1.08-3.05)** | 1.75 (0.99-3.10) | 1.36 (0.74-2.51) |
| Myocardial infarction | 3.0 | 4.2 | 0.24 | 1.24 (0.69-2.26) | 1.23 (0.63-2.41) | 1.05 (0.52-2.16) |
| CHF | 5.3 | 11.8 | <0.0001 | **1.89 (1.26-2.83)** | **2.23 (1.42-3.49)** | 1.59 (0.97-2.60) |
| Stroke | 4.1 | 3.7 | 0.68 | 0.77 (0.42-1.40) | 0.72 (0.34-1.53) | 0.54 (0.24-1.20) |
| Peripheral artheriopathy | 9.8 | 16.1 | 0.0006 | **1.45 (1.03-2.03)** | **1.70 (1.18-2.47)** | **2.10 (1.41-3.12)** |
| Hypertension | 46.0 | 64.8 | <0.0001 | **2.19 (1.73-2.78)** | **2.15 (1.66-2.77)** | **1.93 (1.48-2.51)** |
| **Musculo-skeletal diseases** | | | | | | |
| OA any site | 38.4 | 43.0 | 0.10 | 1.12 (0.89-1.42) | 0.96 (0.74-1.23) | 1.10 (0.85-1.45) |
| Hand OA | 20.3 | 22.8 | 0.30 | 1.10 (0.84-1.45) | 1.13 (0.85-1.52) | **1.52 (1.12-2.08)** |
| Knee OA | 24.3 | 30.1 | 0.02 | 1.20 (0.93-1.55) | 0.89 (0.67-1.18) | 0.99 (0.74-1.34) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hip OA | 12.3 | 16.0 | 0.06 | 1.21 (0.88-1.67) | 1.09 (0.77-1.54) | 1.20 (0.83-1.74) |
| Chondrocalcinosis | 6.6 | 7.3 | 0.63 | 1.05 (0.67-1.63) | 1.04 (0.66-1.65) | 0.96 (0.59-1.56) |
| Inflammatory arthritis | 0.9 | 0.5 | 0.75 | 0.62 (1.14-2.79) | 0.76 (0.16-3.58) | 1.39 (0.28-6.86) |
| Hip replacement | 4.2 | 4.5 | 0.83 | 0.96 (0.55-1.68) | 0.93 (0.51-1.71) | 1.03 (0.53-1.90) |
| Analg drug use (knee pain) | 24.6 | 24.9 | 0.92 | 1.00 (0.77-1.30) | 0.84 (0.63-1.12) | 0.89 (0.66-1.20) |
| Analg drug use (hip pain) | 19.3 | 20.9 | 0.47 | 1.09 (0.82-1.45) | 0.95 (0.70-1.29) | 1.02 (0.74-1.41) |
| Osteoporosis | 55.5 | 48.3 | 0.01 | **0.66 (0.52-0.84)** | **0.74 (0.57-0.96)** | **0.69 (0.53-0.91)** |
| femoral fracture | 4.8 | 5.3 | 0.70 | 0.88 (0.52-1.49) | 1.05 (0.56-1.95) | 1.12 (0.58-2.18) |
| vertebral fracture | 1.5 | 1.1 | 0.51 | 0.59 (0.20-1.74) | 0.68 (0.22-2.07) | 0.75 (0.23-2.40) |
| Disability in >1 ADL | 24.7 | 36.0 | <0.0001 | **1.37 (1.05-1.79)** | **1.35 (1.01-1.79)** | 1.31 (0.97-1.78) |
| Edentulism | 43.2 | 50.8 | 0.008 | 1.21 (0.95-1.52) | 1.27 (0.99-1.63) | **1.31 (1.01-1.71)** |
| **Neurological disorders** | | | | | | |
| Parkinson’s disease | 1.4 | 0.8 | 0.60 | 0.45 (0.14-1.61) | 0.50 (0.14-1.78) | 0.37 (0.09-1.33) |
| Depression | 20.7 | 23.2 | 0.32 | 1.07 (0.80-1.44) | 1.20 (0.88-1.63) | 1.27 (0.91-1.74) |
| Cognitive impairment | 9.9 | 14.4 | 0.01 | 1.04 (0.71-1.54) | 1.11 (0.70-1.76) | 0.95 (0.57-1.56) |
| **Metabolic and other morbid** | | | | | | |

| **conditions** | | | | | | |
|---|---|---|---|---|---|---|
| Dyslipidemia | 42.0 | 41.8 | 0.95 | 1.14 (0.88-1.45) | 1.15 (0.88-1.50) | 1.14 (0.87-1.51) |
| COPD | 4.9 | 5.0 | 0.95 | 0.98 (0.58-1.65) | 1.06 (0.62-1.83) | 1.00 (0.56-1.78) |
| Diabetes | 10.5 | 11.5 | 0.44 | 1.05 (0.73-1.51) | 0.85 (0.57-1.26) | 0.81 (0.53-1.22) |
| Neoplasms | 7.0 | 6.8 | 0.91 | 0.93 (0.59-1.47) | 0.93 (0.56-1.55) | 0.82 (0.48-1.40) |

| Males | CTR | HU | p | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|---|
| **Cardio vascular diseases** | | | | | | |
| Any CVD | 51.7 | 72.4 | <0.0001 | **2.40 (1.69-3.40)** | **2.32 (1.62-3.33)** | **2.00 (1.38-2.90)** |
| Angina | 4.3 | 6.5 | 0.19 | 1.61 (0.83-3.13) | 1.42 (0.71-2.84) | 1.36 (0.74-2.51) |
| Myocardial infarction | 5.2 | 9.8 | 0.02 | **1.99 (1.13-3.49)** | **2.07 (1.16-3.68)** | 1.67 (0.92-3.05) |
| CHF | 4.5 | 12.5 | <0.0001 | **2.85 (1.66-4.91)** | **2.86 (1.59-5.13)** | **2.23 (1.21-4.14)** |
| Stroke | 4.7 | 9.8 | 0.005 | **2.07 (1.17-3.68)** | **2.00 (1.02-3.89)** | 1.57 (0.78-3.18) |
| Peripheral artheriopathy | 18.4 | 29.4 | 0.0006 | **1.78 (1.24-2.55)** | **1.78 (1.21-2.60)** | **1.67 (1.12-2.48)** |
| Hypertension | 35.1 | 46.7 | 0.003 | **1.62 (1.18-2.23)** | **1.60 (1.15-2.23)** | **1.45 (1.03-2.04)** |
| **Musculo-skeletal diseases** | | | | | | |
| OA any site | 25.4 | 28.8 | 0.33 | 1.14 (0.80-1.63) | 1.09 (0.75-1.57) | 1.32 (0.90-1.93) |
| Hand OA | 15.9 | 16.3 | 0.88 | 0.98 (0.64-1.51) | 1.00 (0.65-1.56) | 1.38 (0.87-2.19) |
| Knee OA | 10.5 | 16.3 | 0.02 | **1.58 (1.02-2.47)** | 1.44 (0.91-2.28) | **1.72 (1.06-2.79)** |
| Hip OA | 8.2 | 6.5 | 0.44 | 0.74 (0.40-1.39) | 0.66 (0.33-1.31) | 0.63 (0.31-1.28) |
| Chondrocalcinosis | 3.9 | 3.8 | 0.95 | 0.91 (0.40-2.08) | 0.88 (0.38-2.02) | 0.92 (0.39-2.19) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Inflammatory arthritis | 0.1 | 1.6 | 0.01 | **16.66 (1.71-161.88)** | **33.67 (3.00-377.91)** | **42.01 (5.47-322.39)** |
| Hip replacement | 2.0 | 2.2 | 0.78 | 1.06 (0.36-3.15) | 1.14 (0.38-3.45) | 1.21 (0.39-3.81) |
| Analg drug use (knee pain) | 10.2 | 13.6 | 0.18 | 1.35 (0.85-2.16) | 1.13 (0.68-1.87) | 1.14 (0.67-1.91) |
| Analg drug use (hip pain) | 8.3 | 10.3 | 0.37 | 1.24 (0.73-2.10) | 1.13 (0.64-1.97) | 1.04 (0.58-1.86) |
| Osteoporosis | 24.2 | 22.8 | 0.70 | 0.86 (0.59-1.26) | 1.01 (0.68-1.49) | 0.95 (0.63-1.43) |
| femoral fracture | 3.3 | 2.2 | 0.41 | 0.65 (0.23-1.85) | 0.39 (0.09-1.67) | 0.44 (0.10-1.93) |
| vertebral fracture | 0.4 | 1.1 | 0.24 | 2.46 (0.45-13.64) | 1.21 (0.13-11.22) | 0.94 (0.09-9.60) |
| Disability in >1 ADL | 18.0 | 26.6 | 0.006 | 1.55 (1.05-2.28) | 1.44 (0.94-2.20) | 1.41 (0.91-2.20) |
| Edentulism | 40.9 | 45.6 | 0.17 | 1.17 (0.85-1.63) | 1.19 (0.85-1.67) | 1.17 (0.82-1.66) |
| **Neurological disorders** | | | | | | |
| Parkinson's disease | 1.4 | 1.1 | 0.99 | 0.71 (0.16-3.17) | 0.87 (0.19-3.99) | 0.72 (0.15-3.50) |
| Depression | 8.8 | 9.9 | 0.64 | 1.09 (0.62-1.92) | 1.02 (0.55-1.91) | 1.10 (0.58-2.11) |
| Cognitive impairment | 8.6 | 8.7 | 0.98 | 0.85 (0.47-1.55) | 0.80 (0.39-1.67) | 0.73 (0.34-1.57) |
| **Metabolic and other morbid conditions** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Dyslipidemia | 27.8 | 34.6 | 0.08 | **1.56 (1.08-2.26)** | **1.53 (1.06-2.23)** | 1.40 (0.95-2.06) |
| COPD | 15.1 | 22.8 | 0.01 | **1.59 (1.07-2.34)** | **1.62 (1.07-2.44)** | **1.60 (1.04-2.45)** |
| Diabetes | 8.4 | 6.0 | 0.27 | 0.71 (0.37-1.35) | 0.64 (0.33-1.25) | 0.55 (0.283-1.07) |
| Neoplasms | 8.0 | 10.9 | 0.20 | 1.37 (0.82-2.30) | 1.38 (0.79-2.38) | 1.09 (0.61-1.93) |

**Table 3**. HU prevalence and ORs (95%CI) by comorbidity class and gender

| | number of comorbidities | n | HU prevalence N (%) | adjusted OR* | 95% CI | Adjusted p-value* |
|---|---|---|---|---|---|---|
| WOMEN | | | | | | |
| | 0 | 185 | 23 (12.4) | 1 (reference) | | 0.32 |
| | 1-3 | 1402 | 304 (21.7) | 1.48 | 0.88 – 2.52 | |
| | ≥4 | 216 | 57 (26.4) | 1.53 | 0.80 – 2.89 | |
| | | | | | | |
| | | | | | | |
| MEN | | | | | | |
| | 0 | 250 | 18 (7.2) | 1 (reference) | | 0.007 |
| | 1-3 | 862 | 149 (17.3) | **2.40** | **1.38 – 4.08** | |
| | ≥4 | 108 | 23 (21.3) | **2.54** | **1.21 – 5.37** | |
| | | | | | | |

*Adjusted for: Age, BMI and eGFR