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PREVALENCE OF VERTEBRAL FRACTURE AND DENSITOMETRIC OSTEOPOROSIS IN SPANISH ADULT MEN. THE CAMARGO COHORT STUDY.

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PREVALENCE OF VERTEBRAL FRACTURE AND DENSITOMETRIC OSTEOPOROSIS IN SPANISH ADULT MEN. THE CAMARGO COHORT STUDY

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Abstract.

The aim of this study was to assess the prevalence of densitometric osteoporosis and vertebral fractures in Spanish men ≥ 50 years, and to study how the relationship between them may change depending on how osteoporosis is diagnosed. A community-based population of 1003 men ≥50 yrs. was studied. BMD (lumbar spine, femoral neck, total hip) was determined by DXA. Vertebral fractures were assessed by lateral thoracic and lumbar spine radiographs. The prevalence of osteoporosis was estimated with both the WHO (T-score <-2.5 at the femoral neck, calculated using the young white female normal reference database) and the NOF criteria (T-score <-2.5 at the femoral neck, total hip or lumbar spine, calculated using the young white male normal reference). The prevalence of osteoporosis using the WHO criterion was 1.1%, and the NOF criterion 13%. That of vertebral fractures was 21.3%. The AUC for the relationship between BMD and vertebral fracture prevalence was 0.64.The OR for osteoporosis by WHO definition was 2.57 (p=0.13), and by NOF definition 1.78 (p=0.007). Vertebral fracture prevalence rose with age. The prevalence of osteoporosis increased only moderatly in men over 70 with the WHO criterion, and showed no change with the NOF definition. The prevalence of osteoporosis by using the WHO definition in Spanish men is too small to have any meaningful clinical use. The figure is greater with the NOF definition, but in any case, it would seem that population-based studies of BMD in men are of questionable value.

1. Introduction.

Osteoporosis is a major public health problem that affects not only postmenopausal and elderly women, but also men (1). About 25-30% of osteoporotic fractures occur in males, and their morbidity and mortality, at least after hip fracture, are greater in men than in women (2). Nevertheless, male osteoporosis has been much less studied than postmenopausal osteoporosis, and its epidemiology is worse known (1,3). Notably, studies on the prevalence of male densitometric osteoporosis have often led to conflicting results (4-15). The discrepancies are attributable, at least in part, to the fact that different criteria have been proposed for its diagnosis. Hence the diagnosis of osteoporosis in men as defined by the World Health Organization (WHO) is based on the cut-off value of femoral neck BMD used in women (T score -2.5 at the femoral neck, calculated using the young white female normal reference database) (16). However, the diagnosis of osteoporosis in men as used by the National Osteoporosis Foundation (NOF) is defined as a T-score of -2.5 or lower at the femoral neck, total hip or lumbar spine, calculated from the young white male normal reference database (17). As an example of the difference by using one rather than another definition, the study by Ensrud et al (14) may be cited. In this study 2.2 % or 9.4% of men aged 65 years or over were identified as having osteoporosis according to whether the WHO or the NOF definitions, respectively, were used.

Besides this, discrepancies regarding epidemiological data on male osteoporosis may be related to factors other than osteoporosis definition, such as secular changes, the country where the study is carried out, the age of the population assessed and, ultimately, technical and methodological reasons. Looker et al. (6), with the WHO definition, reported a 2% osteoporosis prevalence in men aged 50 years and older in the National Health and Nutrition Examination Survey [NHANES] carried out the years 2005-2006, whereas the figure was 4% in those from the NHANES III study, which had been conducted in the years 1988-1994 (5). The prevalence of osteoporosis reported in Sweden in the year 2000 in men 50-84 years with the WHO definition was 6.3% (18).

This study shows a prevalence of 7.8% in men 70-79 years old, and of 16.6% in men 80-84 years old.

Some controversy exists also regarding vertebral fracture prevalence in men. Again, discrepancies may be attributed to the different criteria used to identify a vertebral fracture. For instance, the European Vertebral Osteoporosis Study (EVOS) (19) showed that age-standardized vertebral fracture prevalence across Europe was 12.2% when assessed by the McCloskey et al. (20) method, and 20.2% when estimated with the method of Eastell et al. (21). These discrepancies may decrease if a specific definition of vertebral fracture becomes the standard approach, as seems to be the case with the method of Genant et al. (22), which is being widely accepted at the present time. However, the subjective nature of the X-ray reading makes hardly avoidable that the results can vary from one study to another. In addition to this, other factors such as the age and the place of the population studied, may justify some of the differences reported on the prevalence of vertebral fractures.

Since the male prevalence of both densitometric osteoporosis and vertebral fractures differs with their definition and the other mentioned factors, such as the place and maybe even the timing of the study, we have found of interest to report our experience on this issue, with the aim of providing new information on the subject. This may be of particular relevance given the scarcity of information that exists in this regard in the Mediterranean countries, and more specifically in Spain.

2. Methods

2.1. Study design and participants

The study population consists of the men enrolled in the Camargo Cohort Study. Full details of this cohort have been previously reported (23, 24). Briefly, this cohort was set up with postmenopausal women and men aged 50 years or older attending a Primary Care Center in Northern Spain (Camargo, Cantabria) for medical reasons or for their regular programmed health check, whichever happened first. When potential participants did not come to their Primary Care

Center for any of those reasons during the period of recruitment, they were located by phone and invited to participate. All participants were white, as are more than 95% of people in our region (Cantabria). Exclusion criteria were either having the principal residence outside the region or having experienced a trauma which could call into question the fragility nature of the fractures. Being unable to attend the recruiting Primary Care Center or to undergo the planned tests were other exclusion criteria. The study was approved by the local Ethics Committee, (Comité Ético de Investigación Clínica de Cantabria-IDIVAL. Internal code: 2014.155), and all subjects gave written informed consent.

At the baseline visit, men were interviewed and all participants provided data regarding risk factors for osteoporosis and fractures following a structured questionnaire (Supplemental data, Appendix A).

2.2. Laboratory measurements

Blood samples were obtained from an antecubital vein in the morning. Routine biochemical parameters were measured by standard automated methods in an ADVIA 2400 Chemistry System autoanalyser (Siemens Healthcare Diagnosis, Eschborn, Germany).

2.3. Bone mineral density assessment and osteoporosis definition

BMD was measured by DXA (Hologic QDR 4500, Bedford, MA, USA) at the lumbar spine (L2-L4), femoral neck, and total hip. *In-vivo* precision was 0.4-1.5% at the different measurement sites. Results were expressed as gr/cm^2 and as T-score. The prevalence of osteoporosis was estimated in two ways. First, as a T score -2.5 or lower at the femoral neck calculated using the young white female normal reference data base (WHO definition). Second, as a T-score of -2.5 or lower at the femoral neck, total hip or lumbar spine, calculated using the young white male normal reference base (referred to as NOF definition). Lumbar spine reference values were obtained from the study conducted in a Spanish population by Díaz-Curiel et al. (9) (1.039 ± 0.120 mg/cm^2 for men). Those for the hip were taken from the NHANES III reference database (5). Quality control was performed according to the usual standards (25).

2.4. Vertebral fracture assessment

Thoracic and lumbar X-rays were taken, centered at the T7 and L3 vertebrae respectively. Vertebral fractures were identified according to the method of Genant et al. (22). Radiographs were reviewed independently by two of the authors, blinded to any other clinical data. Disagreements were resolved by consensus. Hereafter we refer to grade 1 fractures (loss of vertebral height between 20 and 25%) as "mild", grade 2 (loss between 25 and 40%) as "moderate", and grade 3 (loss greater than 40%) as "severe".

2.5. Statistical analysis

Results were expressed as mean ± SD or percentages, as appropriate. The prevalence of both vertebral fractures and densitometric osteoporosis was adjusted by age to the whole Camargo population of men aged 50 years or older, according to the 2011 population registry of the area. A multivariate logistic regression was performed to assess the independent effect of osteoporosis (defined either with the WHO or with the NOF criteria) on the prevalence of vertebral fractures, estimating the corresponding odds ratios (OR). The area under the ROC curves (AUC) plotting the BMD femoral neck against the vertebral fractures prevalence was also calculated.

3. Results

A total of 1,003 out of 1,110 identified eligible men (90.4%) were recruited (Supplemental data, Figure 1). Their baseline characteristics are shown in table 1. As can be seen, only 20 patients (2% of men) were receiving treatment for osteoporosis (17 bisphosphonates, 2 calcitonin and 1 strontium ranelate)".

3.1. Osteoporosis prevalence

When diagnosed with the WHO definition, the prevalence of osteoporosis was 1.1% [95%CI, 0.4-1.8]. With the NOF definiton, this prevalence was 13.0% [95%CI, 10.8-15.0] (Table 2). There were marked differences between the proportion of participants with BMD $\leq$ -2.5 SD (male T-score) at the spine (11.7%; 95%CI, 9.6-13.7), at the femoral neck (2.4%; 95%CI, 1.4-3.4) and at the total hip (0.6%; 95%CI, 0.1-1.1). Therefore, with the gender specific T-score, the prevalence of osteoporosis in our study population was about five times higher at the spine than at the femoral neck. The percentage of men with a T-score -2.5 or lower at the femoral neck was more than twice as high when the T-score was calculated with the male reference than when it was with the female (2.4% and 1.1% respectively).

3.2. Vertebral fracture prevalence

The overall prevalence of radiographic vertebral fractures was 21.3% [95%CI, 18.7-23.9], and that of moderate and severe fractures together, 6.7% [95%CI, 5.1-8.3] (5.1% [95%CI 3.7-6.5] for moderate and 1.6% [95%CI, 0.8-2.4] for severe fractures).

3.3. Changes over time

The prevalence of all vertebral fractures rose with age from 12.9% (95%CI, 6.4-19.5) in men 50-54 years to 32.6% (95%CI 25.4-39.8) in men over 74. Moderate and severe fracture prevalence also increased from 1.8% (95%CI, 0.2-6.1) to 10.7% (95%CI, 5.9-15.5) (Table 3, Fig. 1). These figures are in sharp contrast with the absence or virtually absent increase in densitometric osteoporosis with ageing. No change was observed until late in life (over 70 with the WHO definition and over 75 with that of the NOF) (Table 2). Such modest changes reflect the small modification in BMD with age. A slight decrease of femoral neck BMD was noted in men 75 years or older ($p<0.01$). Curiously enough, at the lumbar spine, a small non-significant age-related gain was observed (Fig 2). This could probably be interpreted as due to osteoarthritis development with age.

3.4. Univariable and multivariable analysis

The mean value of BMD at the femoral neck in men with vertebral fracture was 0.793(± 0.129) g/cm^2, and in those without 0.825(± 0.120) g/cm^2 [p<0.001]. This results in a difference of 3.8%, which represents 0.27 SD. The corresponding figures at the spine were 0.963(± 0.154) and 1.035(±0.155) g/cm^2 [p<0.001], the difference being 7%, which represents 0.46 SD. At the total hip they were 0.942(±142 g/cm^2) and 0.986(±0.121 g/cm^2) [p<0.001], which means a difference of 4.5%, equivalent to 0.34 SD.

In the multivariable analysis, after controlling for potential confounding factors (age, weight, height, BMI, education level, exercise, family history of hip fracture, smoking and alcohol intake, dairy calcium intake, number of falls in the previous year, causes of secondary osteoporosis and chronic diseases), it was found that, when defining osteoporosis with the NOF criterion, the presence of osteoporosis, along with age and history of previous fracture, remained independently associated with prevalent vertebral fractures, the OR being 1.78 (95%CI, 1.17-2.72; p=0.007). However, when the same analysis was performed defining osteoporosis with the WHO criterion, the corresponding OR for osteoporosis was non-significant: 2.57 (CI: 0.75-8.85; p: 0.13).

3.5. Area under the ROC curves.

The AUC for the relationship between femoral neck BMD and vertebral fracture prevalence was 0.64. In order to determine whether using the -2.5 female T-score as a cutoff value behaves better than the -2.5 male T-score, the operating characteristics of each of them were studied (Table 4). As can be seen, there were practically no differences between the sensitivity, specificity, positive and negative predictive values, or positive and negative likelihood ratios, determined with both criteria

4. Discussion

The prevalence of male osteoporosis in our study population, as defined with the WHO criterion (16), was only of 1.1%. With the NOF criterion (17) it rose to 13%. The prevalence of all vertebral fractures as a whole was 21.3%,

and that of moderate or severe fractures considered together 6.7%. Vertebral fracture prevalence increased with age, while densitometric osteoporosis prevalence remained unchanged until late in life (over 70-75 years).

Worldwide studies on the prevalence of densitometric osteoporosis in men have led to conflicting results. The main reason is the double debate about whether BMD must be measured only at the femoral neck, or also at the spine and the total hip, and about whether a male or female reference must be used. The WHO supports the measurement of BMD at the femoral neck and the use of the cut-off value established for women (T-score -2.5 calculated with the young white female normal reference database) (16). Instead, the NOF advocates the measurement at the three sites, with a T score threshold of -2.5 as calculated with the young white male normal reference data base (17). The use of one or another definition may imply big differences in the prevalence of osteoporosis. For instance, Ensrud et al. (14) have reported in men aged 65 years or over a prevalence of 2.2 % with the WHO definition, and of 9.4% with that of the NOF. In our own study, carried out in men aged 50 years or over, the corresponding figures were 1.1% and 13%. With the WHO definition Looker et al. have reported a 2% osteoporosis prevalence in men aged 50 years and older in the NHANES study carried out in the years 2005-2006 (6). Curiously, the figure had been 4% in the previous NHANES III study (1988-1994) (5). In a Swedish study published in 2000, the prevalence of osteoporosis, defined in the same way, in men 50-84 years was 6.3% (18). Therefore, not only is the prevalence of osteoporosis higher when the NOF definition, instead of that of the WHO, is used, but besides that, other factors such as the year and the place of the study may also contribute to the variability (26,27). In fact, we have just seen in the figures commented on above that the prevalence, defined with the same WHO criterion, ranges from 1.1 % in our own study, up to 6.3 in that reported from Sweden, with intermediate values in the NHANES studies. Of note, our results suggest that Spanish prevalence of osteoporosis at the femoral neck is lower than that of men from either the United States or from Sweden. Such findings did not surprise us, since hip fracture incidence is also lower in Spain than in either of these countries. According to information published by

the WHO (28) and by the IOF (29), Swedish people suffer about 2.5-3.0 times more hip fractures than Spanish people, and people from the US, about 1.2-1.4 times more, ratios that apply to both men and women.

Osteoporosis may be diagnosed either on a clinical (the presence of a fragility fracture) or densitometric basis. If diagnosed on clinical basis, at least 21% of the men in our study have osteoporosis. This is in sharp contrast with the figure provided by the WHO definition, which is about twenty times smaller (1.1%). This discrepancy raises questions about the clinical utility of measuring BMD in men applying the WHO definition, since the percentage of men classified as osteoporotic would be too low to have any clinical meaning. Even the use of a gender specific T-score when measuring BMD at the femoral neck would not be of much help, since the percentage of men diagnosed as osteoporotic would only be of 2.4%. Furthermore, the AUC relating femoral neck BMD and the prevalence of vertebral fractures in our study is only 0.64. On the other hand, the adjusted OR for the WHO definition is not significant (2.57 [CI: 0.75-8.85; p: 0.13]).

Interestingly enough, the adjusted OR for the NOF definition however is indeed significant (1.78; 95%CI, 1.17-2.72; p=0.007). This difference must be attributed to the fact that, contrary to what happens with BMD at the femoral neck, the NOF definition includes BMD at the spine, and there is a better relationship between the spine BMD and vertebral fractures than between these fractures and femoral neck BMD. In this regard, it is worth taking into account that the rationale under the WHO definition is the claim that the relationship between areal BMD and fracture risk is the same in men as in women when adjusted by age (30), a statement that may be right when BMD is measured at the femoral neck and the location of the fractures considered is the hip. However, this may not hold true for the relationship between femoral neck BMD and vertebral fractures (31). To establish the risk of vertebral fracture, a procedure that includes spine BMD is preferable, as is the case with the NOF definition.

As previously stated, the AUC was 0.64. For the sake of comparison, we also assessed the AUC in the women of the same cohort (the Camargo

Cohort), the figure being clearly greater: 0.77. This result highlights another interesting concept: namely, that the association of BMD with vertebral fractures is stronger in women than in men. One factor that may help explain this difference is the fact that men experience more trauma through their lives, related to a higher degree of physical activity than women. In women though, fractures would seem to keep a closer relationship with the decrease in bone mass than with suffering from trauma. In the later stages of life, however, there is an increase in the tendency to fall in both men and women, so that by this time the traumatic component is common to both sexes.

The prevalence of vertebral fractures reported by different studies has been, similarly to what has been said above for densitometric osteoporosis, quite variable (20,21,32,33). Again, the main reason is that several methods have been in use. Other factors, such as the type of population and the place of study, may also play a role. A fact that is important to underline is that the assessment of a vertebral fracture has an element of subjectivity that is not present in BMD measurement, since DXA provides a very objective result, hardly susceptible to influence by personal biases. For these reasons, comparing our results on vertebral fracture prevalence with those from other studies is a task that entails uncertainty and questionable conclusions. Another Spanish study (32) also carried out with the Genant method, reported a prevalence of 20.8% (CI 95% 13.4-29.9%), close to ours. However, a recent publication by Ensrud et al. (33) performed in the United States again using the Genant method estimates a prevalence of only 11.1%. In an accompanying editorial, Briot et al. (34) comment on the fact that the authors evaluate the presence of fractures after a triage performed by trained technicians and that although such triage is described as reliable, not much information is given about it. Clearly, more objective methods of evaluating vertebral fracture prevalence are needed before general statements about its epidemiology may be made. Other definitions of vertebral fracture, such as those of Eastell et al. (21) or McCloskey et al. (20) provide results which, although different, are also in a range (10-25%) well above the percentages of male osteoporotic population established by the WHO definition (16). Variability therefore in the

prevalence of vertebral fractures provided by the different methods do not contradict the idea that the WHO definition of male osteoporosis is of little clinical value in establishing the risk of vertebral fractures.

Our study has some limitations. First, the Camargo cohort is derived from a single geographic region of Spain, and therefore, perhaps our findings cannot be extrapolated to other populations. Second, it is a cross-sectional study. However, the location of the fracture considered (vertebrae) hinders a prospective study. Among the strengths we want to emphasize, it is worth mentioning that the sample was large enough (more than 1000 men), the participants were well-characterized, and all BMD measurements were done with the same device. In addition, the presence of women in the Camargo Cohort allowed us to perform some comparative studies.

To conclude, in Spain the WHO definition classifies as osteoporosis a proportion of men too small to be of much clinical utility. The figure is far lower than that of osteoporosis defined on clinical grounds, by the presence of fractures. In this regard, the NOF definition may be preferable, since by including BMD measurement at both the spine and the hip, it has a greater ability to predict the development of fractures in different locations. In any case, the relationship between BMD and vertebral fractures is lower in men than in women, so that BMD is not such a useful tool in the former as it is in the latter. In fact, in men such study may make sense only for those over 70-75 years.

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Conflict of ineterest

All authors declare that they have no conflicts of interest.

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Figure 1: Distribution of prevalent vertebral fractures (%) in men, stratified by age.

Figure 2: Mean BMD at lumbar spine (LS), femoral neck (FN) and total hip (TH) by age subgroups.

(*): A decrease of femoral neck BMD was noted in men 75 years or older ($p<0.01$)

Table 1. Baseline epidemiological characteristics, laboratory parameters and bone mineral density (BMD) in adult men.

Parameter	**Mean±SD or %** (n=1,003)
Age (years)	65 ± 9
Weight (Kg)	82 ± 12
Height (cm)	168 ± 6
BMI (Kg/m^2)	29.0± 3.5
Waist perimeter (cm)	102 ± 9
Arm spam (cm)	172 ± 9
History of falls (last year) (%)	15
Any fracture > 40 ys (%)	16
Physical activity	
- Sedentarism (%)	1
- Moderate (%)	31
- High (%)	68
Current smoking (%)	19
Current alcohol consumption (%)	50
Dairy calcium consumption (mg/day)	500 (300-700)*
Education (yrs)	8 (8-10)*
Dyslipidemia (%)	35
Diabetes mellitus (%)	19
Hypertension (%)	50
Calcium supplements (%)	2
Vitamin D supplements (%)	2
Anti-osteoporosis treatment (%)	2
Glucose (mg/dl)	103 ± 24
Creatinine (mg/dl)	1.1 ± 0.2
eGFR (ml/min/1.72m^2)	77.4 (67.5-9.6)*
cCa (mg/dl)	9.2 ± 0.3
Phosphate (mg/dl)	3.1 ± 0.5
Albumin (g/L)	44 ± 3
Alkaline phosphatase (U/L)	65 (54-68)*

BMD, LS (g/cm^2)	1.019 ± 0.158
BMD, LS (T-score)	-0.86 ± 1.44
BMD, LS (Z-score)	0.06 ± 1.49
BMD, FN (g/cm^2)	0.818 ± 0.122
BMD, FN (T-score)	-0.81 ± 0.91
BMD, FN (Z-score)	0.27± 0.91
BMD, TH (g/cm^2)	0.977 ± 0.127
BMD, TH (T-score)	-0.36 ± 0.85
BMD, TH (Z-score)	0.24 ± 0.87

*Median (interquartile range)

cCa: Albumin-corrected serum total calcium; eGFR: Estimated glomerular filtration rate, BMD: Bone mineral density, LS: lumbar spine; FN: femoral neck; TH: total hip. T-score: number of standard deviations (SDs) below the mean value of young men; Z-score: number of SDs below the mean of men of the same age.

Table 2. Prevalence of men (%) with osteoporosis according to WHO and NOF definitions.

Age group	n	WHO definition	NOF definition
50-54	116	1.7	11.3
55-59	209	0.5	11.9
60-64	219	0.9	12.6
65-69	165	0.6	13.8
70-74	116	2.7	10.3
≥75	178	1.8	16.5
Total	**1003**	**1.1**	**13.0**

Table 3. Prevalence of men (%) with vertebral fracture by age group.

Age group	n	All	Moderate	Severe
50-54	116	12.9	0.9	0.9
55-59	209	17.2	4.8	1.0
60-64	219	20.1	5.5	0.5
65-69	165	19.4	4.2	3.0
70-74	116	25.0	6.9	0.9
≥75	178	32.6	7.3	3.4
Total	**1003**	**21.3**	**5.1**	**1.6**

Table 4. Operative characteristics of femoral neck BMD at two threshold values: T-score -2.5 calculated using the young white female normal reference database (WHO definition of osteoporosis) and T-score -2.5 calculated using the young white male normal reference database.

	Female -2.5 T-score	**Male -2.5 T-score**
Sensitivity (95% CI)	2.4% (0.08-4.7)	4.8% (1.6-7.9)
Specificity (95% CI)	99% (98.5-99.9)	98% (97.2-99.2)
Positive predictive value (95% CI)	45% (11.5-79.4)	42% (19.9-63.5)
Negative predictive value (95% CI)	79% (76.3-81.5)	79% (76.7-81.9)
Positive likelihood ratio (95% CI)	3.1 (0.9-9.9)	2.7 (1.2-5.9)
Negative likelihood ratio (95% CI)	0.98 (0.96-1.01)	0.97 (0.94-1.00)

CI: Confidence interval

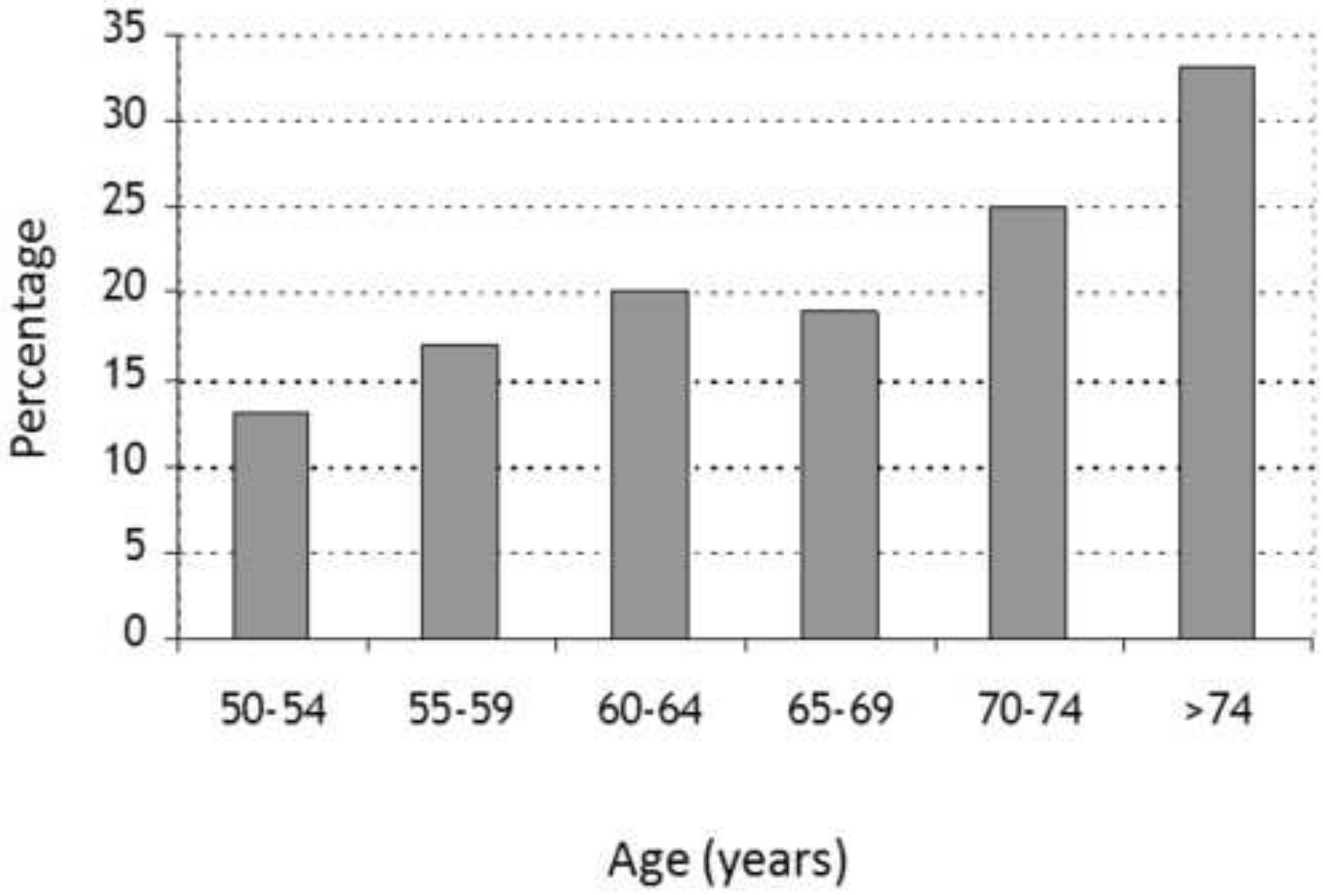

Figure 1

Figure 2