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Planning a sample for an epidemiological survey

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Abstract

This work illustrates the joint use of a pilot study and an administrative data base for designing a probabilistic sample for an epidemiological survey. The target is to estimate the prevalence of an asymptomatic disease, the aortic valve stenosis (AS), in the elderly population of the city of Bologna, Italy. The novelty of the study is to reach the target population of elderly patients via a sample of their general practitioners (GPs). The pilot study was conducted in San Giovanni in Persiceto, a town in the province of Bologna. Overall information on patients and their GPs are available in the Azienda Unità Sanitaria Locale di Bologna (AUSL) data sets. Since the disease is asymptomatic, the sampling plan is designed to estimate the number of suspected patients that will be sent to further echocardiographic (ECO) examination. The probabilistic sampling plan aims at controlling the sources of randomness, via an appropriate clustering of the population of GPs. The number of practitioners to sample is fixed in advance. The subpopulations of patients to screen are also defined in advance and assigned to doctors. In this way the potential sources of randomness, due to the individual choices of doctors out of the definition of the experiment, are avoided. The number of elderly patients per doctor has been identified, from the pilot study, as an important factor able to influence the proportion of suspected patients sent to further examination. This feature is the leading factor of the sampling design, together with the clustering of the AUSL Bologna territory in NCPs, which emerges from the AUSL data set.

Keywords

survey sampling, ratio and regression sampling estimator, finite population, epidemiology, cardiology

Abbreviations

AS – aortic valve stenosis, AP – angina pectoris, AUSL - Azienda Unità Sanitaria Locale di Bologna, Italy, ECO examination – ecocardiographical examination, ELISA (Epidemiologia e Livelli di Autosufficienza della Stenosi Aortica) study, NCP (Nuclei di Cure Primarie); QoL – quality of life

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1. Introduction

ELISA (Epidemiologia e Livelli di Autosufficienza della Stenosi Aortica) project regards an epidemiological study about the prevalence of aortic valve stenosis (AS) and the self-sufficiency of the elderly population in a part of the province of Bologna, Italy. This work proposes a sampling plan for estimating AS prevalence in the city of Bologna on the basis of a pilot study conducted in the town of San Giovanni in Persiceto and of the auxiliary information stored in health administrative archives managed by the Bologna AUSL. The construction of a sample in epidemiological studies is an important issue, and several papers have been written (Rohrig et al., 2009a, 2009b; Donner, 1984) about study planning in this field.

Tools associated to statistical sampling design reveal very important to improve efficiency, reduce subjective bias and maintain the sample size under reasonable limits (Levy et Lemeshow, 2008). Simple random sampling is a standard method for selecting units (animals, human-beings) from a population (Cochran, 1977). The use of auxiliary information can also be exploited for decreasing the uncertainty of results. Any sampling technology, like sensitivity and specificity of the screening test, the minimum expected prevalence of the disease within population, the computation of the required sample size, ought to be defined before survey (Cameron et al., 1998).

The definition of the population of interest and the identification of the way for potentially reaching all its elements is crucial. This is especially true when the aim of the study is the estimation of the prevalence of an asymptomatic disease. Aortic valve stenosis (AS) is one of such asymptomatic diseases. According to the medical standards and guidelines (Baumgartner et al., 2009) the echocardiography (ECO) is the most appropriate method for AS diagnosis. To get the diagnosis in patients with a suspicion of AS it is necessary to reach them and obtain their collaboration in undertaking ECO examination. In this study the focus is on the estimation prevalence of AS in the elderly population in the city of Bologna.

A first epidemiological study for assessing the prevalence of AS in the elderly population has been performed in San Giovanni in Persiceto, a municipality of the province of Bologna. This preliminary study was planned for collecting data on the entire population of elderly residents

via the entire population of GPs. Unfortunately, collaboration wasn't complete. For this reason, results are affected by randomness and statistical inference is needed also for suitable estimates for San Giovanni in Persiceto area.

Conclusions from this pilot study are used as guidelines for a wider sampling plan for the metropolitan area of Bologna, with the aim of estimating the number of suspected AS, and consequently the prevalence of the disease. Indeed we don't expect that features of the small population of San Giovanni in Persiceto substantially differ from those of the greater Bologna. Parallel to the findings of the pilot study, a number of basic auxiliary information at the population level has been provided by the archives provided by the AUSL of Bologna. This is an extensive dataset that links patients to their GPs and has been crucial for planning the sampling design for the city of Bologna.

The present study is innovative since it proposes the construction of a probabilistic sample from the population of the elderly patients reached via a sample of their GPs. This is allowed by the fact that in Italy each resident freely chooses her/his own GP. A careful analysis of a number of joint GPs characteristics is the starting point for developing the complex sampling plan which is illustrated in the last section.

Our sampling design proposal can be extended and adapted to any other health context: a survey on patients via their GPs can be proposed for any epidemiological purpose. The basic frame of GPs, organized as they are associated to AUSL, can be in fact enriched with the characteristics of any population of patients of interest according to any potential request.

The paper is organized as follows. Section 2 illustrates the findings of the pilot study that have been used as a guideline for planning the survey in the city of Bologna. Section 3 describes the characteristics of AUSL data archives and highlights how information on the two populations of doctors and their patients can be summarized for use in epidemiological surveys. Then, Section 4 develops the estimation of the number of patients suspected to have AS in San Giovanni in Persiceto, exploiting the information of AUSL data. Section 5 describes the sampling design and the final proposal of units to sample, after isolating important subpopulations of elderly people in the city. The availability of AUSL archives is fundamental also for this step.

2. The main findings from the ELISA pilot study

ELISA study has been primarily planned to estimate the AS prevalence in the elderly population with age-range between 75 and 95 years in the city of Bologna. According to the current literature, no clinical parameters are known to be related with AS. However, comorbidities are very common in elderly patients and strongly influence the therapeutic decision-making (Faggiano et al., *in press*). In order to get preliminary insights, investigators undertook a preliminary study on the population of San Giovanni in Persiceto, a municipality of about 27,000 people, about 20 km far from Bologna. No assessment of the prevalence of this disease was previously evaluated in this area.

There is still no evidence in the literature about a potential relationship between the severity degree of the disease and the quality of life of patients. GPs' records are the only way to obtain valuable medical information about any population of patients, since we can assume that in Italy GPs cover the entire population. For this reason GPs can be meant as complex units that collect information about the population of elderly. The suggestion of reaching patients via their physicians needed however to be checked. No insight was available about the GPs' collaboration and the subsequent collaboration of the selected patients for further clinical investigation. In the following, we summarize results from the pilot study.

2.1. Important issues for the statistical treatment of ELISA results

The pilot study was mainly undertaken by a group of cardiologists of the Policlinico S.Orsola-Malpighi of Bologna. All GPs in San Giovanni in Persiceto were asked to collaborate at the project. A small part of the population of San Giovanni in Persiceto is in health-care of doctors from other municipalities, while doctors which outpatients' clinic is in San Giovanni in Persiceto have some patients residing in other close municipalities. Doctors were asked to screen elderly resident people with age-range between 75 and 95 years. Identification of AS patients was done in 2 steps: first, GPs clinically screened their patients and categorized them into 5 predefined groups: 1) suspected AS; 2) AS known in medical records; 3) previous aortic valve replacement; 4) no AS

indications; 5) ineligible for the study purpose. Patients with artificial aortic valve weren't examined.

In the second step, patients with known or suspected AS (groups 1 and 2) underwent further echocardiographic examination (ECO) in order to confirm the AS diagnosis. Results from the pilot study confirm the high incidence of asymptomatic AS and the need of a survey in a more extended area for a better estimation of the prevalence.

A total of 2870 elderly patients were included in the preliminary study (Figure 1). From the beginning of the study 2 out of 20 doctors refused to collaborate. The remaining 18 doctors clinically screened their elderly patients.

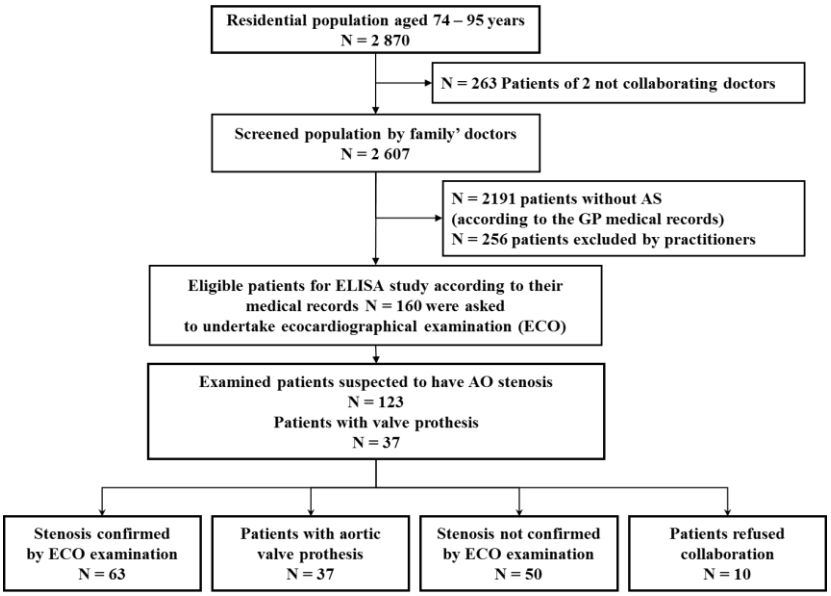

Figure 1. Flow-diagram of ELISA pilot study

Because of the refusal of 2 doctors, information about 263 patients is missing (9.2% of elderly residential inhabitants in San Giovanni in Persiceto). Also, 10 patients (6.3% of those identified as suspected or carriers of prosthetic aortic valve) refused undertake the ECO examination. The lack of collaboration of both GPs and patients induce randomness in the results. Even if small, the values of the two not

collaborating doctors, with their patients, and of not collaborating patients (those refusing to go to the hospital after their doctors' invitation) involve sampling errors that have to be assessed.

2.2. Results from ELISA pilot study: the illness is asymptomatic

According to the current literature, in its early stage AS seems to be an asymptomatic disease. In what follows some analyses are performed in order to check the asymptomaticity of the disease under study.
Basic characteristics of patients, reported in Table A1 in the Appendix, with confirmed or not AS diagnosis, are compared. Patients with aortic valve prosthesis aren't included. No significant difference between the two groups was found, as regards age and presence of comorbidities (peripheral artery disease (PAD) or chronic obstructive pulmonary disease (COPD)) and the variables denoting physical construction. NYHA class III-IV is more present in proportion in the group with AS (moderately significant), where also the mean trans-aortic maximum gradient of 41mmHg was found, identifying a moderate to severe disease burden. No significant differences were found in ECO parameters between groups. In collaboration with the Department of Psychology of the University of Bologna, a smaller subset of 73 screened patients was interviewed for their global assessment of quality of life in order to highlight potential relationships with general health status and clinical presentation (The EuroQol Group, 1990; Brooks, 1996; Pfeiffer, 1995; Zimet et al., 1998; Zigmond et al., 1983). A not statistically significant difference was found between these 2 groups in quality of life general health status (EuroQoL VAS: Visual analogic scale 0-100); the mean of VAS is 67.2 for AS patients and 72.8 for patients without AS. The group of 13 patients with severe grade of AS diagnosis (40-59 mmHg) indicated the worst quality of life: their VAS is 61.2 (not shown in table), although the difference compared with the other patients isn't statistically significant. Deeper investigation on quality of life data for AS patients is needed to highlight the relationship between AS patients and their general status, as regards elderly population.

The most remarkable difference was found in signs of depression (HADS questionnaire, summarized in Table A1, Appendix). Patients with higher age tend to have worst quality of life (measured by EuroQol) and

to be more depressed (measured by HADS depression). These syntheses aren't shown in the table.

No clinical parameter was confirmed as a possible predictive factor of AS diagnosis by univariate logistic regression adjusted for age (partial results shown in Table A2 in the Appendix); these results also confirm accumulation of comorbid diseases in elderly population. However, patients without ECO examination were considered 'disease-free' and seen as the reference population.

2.3. Main conclusions from the pilot study

The main issues emerged from the pilot study follow.

The researchers identified, in this first step, the elderly residents of San Giovanni in Persiceto as the target population instead of the elderly people who are actually followed by practitioners, which might differ since people may choose their doctor irrespective of the municipality of residence. We check, in Section 3, whether this assumption has consequences on the results.

The participation of GPs and suspected patients is incomplete and not managed by the research group. This implies that results are random quantities that need to be associated to their confidence intervals, as illustrated in Section 4.

Since no risk factor for presence of AS has been detected, confirming that the illness is asymptomatic, the assessment of AS prevalence is conditional on identifying suspected cases. A careful random sampling design has therefore to be planned for estimating the number of patients with a suspicion of AS. This will be the focus of the sampling plan illustrated in Section 5.

3. Role of archives

A probabilistic sampling plan needs the knowledge of the target population and the availability of a suitable frame for constructing the sample design that will be used for data collection. An appropriate definition of the target population and the construction of a frame before collecting sampling data give the possibility of controlling the experiment. In this way, further elements of uncertainty, that also ought

to be managed by probability calculus, aren't added during the data collection. For constructing a suitable sampling frame, the appropriate target population is identified from AUSL data.

In Italy, AUSLs dispose of rich data bases containing information on GPs and their patients. These archives, which are updated very frequently and are considered reliable, are constructed for broad administrative and organizational purposes. They are based on the geographical distribution of doctors' out-patients clinics and patients housing. In these archives, any subpopulation of patients can be associated to their GPs.

3.1. The AUSL data-archive

The AUSL datasets cover all municipalities of the province of Bologna except the 10 municipalities belonging to the "circondario di Imola". The 50 municipalities of the AUSL are grouped in 6 districts: "Città di Bologna", "Casalecchio di Reno", Porretta Terme", "San Lazzaro di Savena", "Pianura Est" and "Pianura Ovest". Each district is further partitioned in NCPs (Nuclei di Cure Primarie). These data can be used by researchers without further interviews and are a mean for linking information between GPs and their patients. Such complete archives, updated, for our study, until 31st December 2009, consist of: a) GPs archive, which contains the professional characteristics of physicians such as length of their praxis, type of reached specializations, their time from graduation and their number of patients; b) classification of doctors according to the district of their clinic and the NCP, c) anonymous patients' archive with linkage to his/her GP.

For accomplishing different research purposes, general AUSL archives may be reorganized in the most suitable frame for the appropriate sampling design, according to the aim of the specific study. For the research here illustrated, which aims at estimating the prevalence of an asymptomatic disease in a special subpopulation, the population of elderly patients in the city of Bologna is identified through their GPs. A record linkage with data validation has therefore been performed with this specific purpose, by reorganizing the AUSL archives and selecting the target population of interest in the whole AUSL territory. This process, that characterizes the identification of the target population before designing any sampling design, is described in Figure 2.

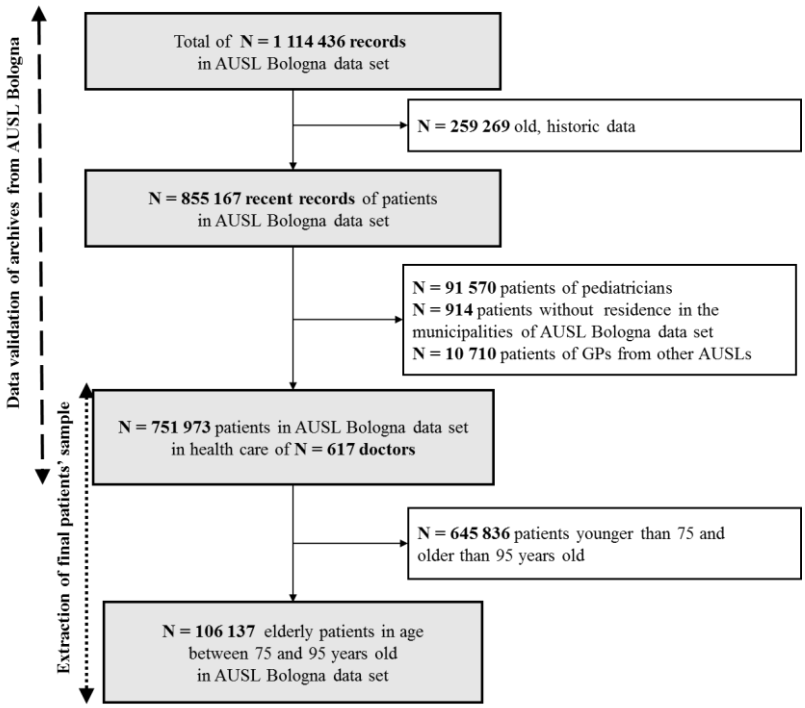

Figure 2. Flow-diagram – AUSL Bologna data set.

From the general AUSL archive, the target population of elderly patients and their doctors is identified. The general data-archives contained 1.114.436 records of patients. We selected the entire population of 751.973 patients of 617 GPs (excluding pediatric patients and patients living outside the AUSL territory with physicians in the territory), and subsequently isolated the target population of 106.137 elderly patients' in age between 75 and 95 years. An analogous data validation of the AUSL archive has to be performed for isolating any other target population for a different purpose.

The distribution of doctors and their elderly patients has been explored for the whole AUSL territory, but also for the city of Bologna and the town of San Giovanni in Persiceto, in order to highlight the main characteristics of the population. Table A3 in the Appendix, which contains the classification into districts, reports some syntheses about the

two populations of practitioners and their elderly patients with the aim of emphasizing the features of doctors that can be relevant for the sampling plan. The town of San Giovanni in Persiceto belongs to the ”Pianura Ovest” district; for this town a dedicated line refers to its 20 doctors in the 3 panels of the table. This information is useful when further discussing the results of the pilot study.

In particular, the first two panels of the table classify, for the AUSL territory, doctors and elderly patients respectively. The classification is done according to a couple of variables, namely the total number of old patients associated to a doctor and various territorial criteria (AUSL considers districts). The number of old patients associated to a doctor is a basic quantity for the objectives of our study. Indeed, the panels of Table A3 highlight that many physicians have many elderly patients, which might cause difficulties in collecting information about the suspected cases. In particular, comparing the area “Città”, referred to the city of Bologna, with the areas ‘Nord’ and ‘Sud’, one sees that the out-patients clinics with more than 250 elderly patients are more concentrated in the city.

Looking at the first panel of Table A3, we see that in the whole AUSL territory 46 doctors have less than 50 old patients, and 283 (45.9%) GPs out of 617 have their out-patients clinic in the city of Bologna. From the second panel of Table A3, one sees that 50.1% (53.132 out of 106.137) of old patients from the whole AUSL territory is concentrated in the city of Bologna. So, the sampling plan for Bologna has to face the issue of many doctors having high number of elderly patients. Also, 1.2% of elderly patients (1.257 out of 106.137) are in charge of practitioners with low number of old patients. In the third panel of Table A3, the percent proportion of elderly patients among the total number of patients per doctor is shown. In average, higher proportions of elderly patients have doctors in the city and the ‘Sud’ area, while in the ‘Nord’ part of the AUSL territory the average proportion is lower.

Some doctors have very few patients. Their exclusion from the sampling frame would lead to the exclusion of a very small number of patients from sampling. A high number of doctors have many patients and, consequently, many old patients. This might influence the quality of their data transmission to the organizers of the sample and the identification of suspected patients.

In the Emilia-Romagna Region, AUSLs organize GPs according to the NCP classification. This organization ought to be respected in the sampling plan. The city of Bologna is administratively organized in 9 quarters. AUSL collapsed the 9 quarters in 5 zones, and further partitioned them in 16 NCPs, according to the scheme of Figure A1 in the Appendix. Deep explorative analyses are performed for the city conditional on the NCP classification, for collecting indications about the sampling plan. In Tables A4 and A5 in the Appendix the distribution of doctors and their patients within the city NCPs is reported, with emphasis on the specialization and the length of praxis of GPs. Specialization and length of praxis might be related to the capability of identifying suspect AS patients. Only specializations in cardiology and geriatrics (Table A4) were taken into consideration as a potential factor that might influence such ability. In the whole city, the average proportion of specialists is 25.2% of GPs and the average proportion of elderly patients is 27.8%. For each NCP group, the proportion of doctors with pertinent specialization among the total of doctors agree with the proportion of their elderly patients among the total of patients: only a few NCPs show statistically significant differences in such proportions. Table A5 shows that for the majority of GPs within each NCP unit the length of praxis is longer than 20 years and quite equal proportion of doctors has praxis shorter, resp. equal or longer, than 30 years. No statistically significant difference was found in the proportion of elderly patients between GPs groups according to the length of praxis (<30 years vs. ≥ 30years) for each NCP unit as well as for the whole city.

In summary, cardiologists and geriatrists don't have higher number of elderly patients than the other GPs and length of praxis of GPs isn't a leading trait for sampling. Therefore, these two characteristics won't be considered as leading factors for sampling.

3.2. Sources of population data and their comparison

In the AUSL archives, patients are associated to the chosen GP, and clustered accordingly. But citizens are usually considered as clustered in the municipality where they live: the number of residents in municipalities is very commonly employed for characterizing the population in a territory. At a given time the total number of people registered in an AUSL doesn't coincide with the total of residents of the

municipalities of the AUSL. We made a number of checks in order to assess whether discrepancies between the population size in municipalities and the number of patients in the corresponding AUSL territory are small and patients' population data in AUSL archives can be considered as roughly equal to the municipal data in the corresponding areas. The response has been, on the whole, positive: differences, in the light of the following comparisons, can be considered as irrelevant.

Since differences are irrelevant, the simplest way to reach patients is through their GPs, instead of through municipal administrative registers. GPs, seen as the target population of complex units, are organized in the AUSL archives.

Differences between demographical administrative datasets and AUSL data (Tables A6 and A7 in the Appendix) about elderly population in the AUSL territory and the city of Bologna are due to different area definitions and borders of units used by different institutions and to different timing in updating archives. We found a difference of 14.942 patients when comparing the whole population of the 50 municipalities of the province of Bologna, without the 10 municipalities of the 'circondario di Imola', from administrative demographical data and AUSL registries (Tables A6 and A7). For the city of Bologna there is a small difference of +180 patients / inhabitants between demographical summaries and AUSL data, including the differences +605 for women and -425 for men. Giving a look at the partitioning in zones, the biggest difference is shown in Savena - S. Stefano (+482) and the smallest in B. Panigale - Reno (-81). Possible explanations of these slight discrepancies are: movement of patients / residents because of work or study, migration of young families from the center to peripheral areas with physician's clinic close to their work. The considerations above, associated with additional age-gender proportions' comparison, allow us to consider the AUSL population of Bologna city as coincident, for practical purposes, with the demographical population.

Similarly, the differences between the number of residential patients per doctor in San Giovanni in Persiceto evaluated respectively by AUSL, administrative records and ELISA selection are also rather small and can be disregarded.

As the main considerations for identifying the target population for the survey are done on the basis of results of the pilot study, we stress that the population of patients isolated for the pilot study is reliable. The main

source of the discrepancies in the total number of old patients between AUSL and San Giovanni in Persiceto's GPs data is due to the definition of target patients' population in the pilot study: GPs were asked to consider only residents. Given the homogeneity of the elderly population in the AUSL territory, there is no evidence of differences between the subpopulation of elderly patients and that of elderly residential patients in the pilot study.

4. Using auxiliary information for calibrating results of San Giovanni in Persiceto

When the practitioners of San Giovanni in Persiceto were asked to collaborate in the pilot study, researchers aimed at a total survey, but, even if collaboration was enthusiastic, the goal wasn't completely achieved, with the consequence that the result of the pilot study has to be considered as a randomly occurring dataset.

Availability of AUSL data revealed a posteriori very fruitful for making conjectures on missing information. Table A8 in the Appendix reports, for each doctor, the summary data on her/his patients. The table shows how each doctor has to be considered as a complex unit and patients as the ultimate units. A main point was to detect whether some individual characteristics of doctors, like their total number of patients, influenced the number of suspected to send to ECO examination.

The second column of the table refers to the values coming from the AUSL archive. The ELISA researchers isolated the total of elderly patients resident in the San Giovanni in Persiceto municipality $t(p)$ (3^{rd} column). The remaining columns refer to the syntheses calculated starting from the volunteer practitioners' data. The headings of some columns are counts: $t(p)$, number of elderly patients; $t(s)$, number of patients suspected to have AS; $t(prot)$, number of patients with aortic valve prothesis; $t(c)$, number of patients with confirmed AS diagnosis; $t(r)$, number of suspected patients refusing collaboration. Some other columns, reporting rates, appear in Table A8: *SR*, rate of suspected patients out of elderly patients; *ProtR*, rate of patients with prothesis out of elderly patients; CR_1, rate of patients with confirmed AS diagnosis out of elderly patients; CR_2, rate of patients with confirmed AS diagnosis among suspected

patients; *RR*, rate of refusing patients among suspected patients; *Prev*, prevalence proportion. Note that *Prev*=((*t*(*prot*) +*t*(*c*))/*t*(*p*)).

Table A8 reports the sample summaries about the 18 collaborating GPs: 2607 resident elderly patients, of which 123 were suspected by GPs and undertook the ECO examination. The diagnosis of AS was confirmed only for 63 patients, 37 patients were reported to have artificial aortic valve and 10 suspected patients refused to continue collaboration. These values have been shown also in Figure 1. The table reports also the sample proportions. The individual proportions CR_2, and their synthesis for all collaborative doctors, are important indicators since they measure the ability of GPs in correctly detecting AS in patients: a value near to 1 would be the best, while, unfortunately, the sample proportion is, in this study, just over 1/2. However, seen under a precautionary perspective (corresponding to a high number of suspected), this value denotes how much the activity of the doctors helps in identifying suspected that end without confirmation of AS diagnosis, being first stage false positive: this is not bad in itself.

All sample counts in the table are denoted in what follows as $t(*)$. Rates can be estimated from sampled data and are denoted as $\hat{p}(*)$. In particular, the rates computed on the basis of the total of eldery patients *SR*, *ProtR*, CR_1 and *Prev* are denoted as $\hat{p}_t(*)$ and the rates computed on the basis of suspected patients CR_2, *RR*, as $\hat{p}_s(*)$.

The information about the total of 20 GPs with more than 50 old patients has been selected from the AUSL archive. The refusal of 2 GPs to participate to the study can be considered as random with respect to the aim of the investigation.

The simplest working hypothesis is that the 18 GPs are randomly selected from the population of 20 doctors. It assumes that the refusal of the two non-collaborating GPs is due to pure chance and isn't related to the object of the study. The proportions computed for the sample can therefore be considered as estimates for the whole population, while estimates of totals need to be calculated with reference to the entire population of 20 GPs.

Table 1 reports the sample standard deviations $s(*)$, which denote high variability, and the sample covariances that characterize the linear links between each measured variable and the number of elderly residential

patients for each doctor $s(*,\hat{p})$. The table contains also the regression coefficients for the whole sample. These values are the basis for the computation of ratio and of regression type finite population estimates and their confidence intervals summarized in Table 2. All sample syntheses are computed also for the two sub-samples of doctors with <150 and ≥150 elderly patients. The differences found between the sub-groups of doctors identified according to their number of elderly patients, suggest us to maintain this difference in the sampling design. Sample covariances and regression coefficients often have opposite signs in the subgroups. When the sign of the synthesis is the same, the strength of the relationship is usually different in the two subgroups.

Indeed, the proportions on the 18 GPs in Table A8 are ratios with random denominator, due to the 2 refusals which were unpredictable before the pilot study. So, sample results need to be considered according to the theory of ratio estimation in finite population sampling.

Proportions computed on sample data and reported in Figure 1 and Table A8, referred to the total of elderly patients, i.e. *SR*, *ProtR*, CR_1 and *Prev*, are:

$$\hat{p}_t(*) = \frac{t(*)}{t(p)} = \frac{t(*)}{2607}$$

and, when computed on the total of suspected, i.e. CR_2 and *RR*, are:

$$\hat{p}_s(*) = \frac{t(*)}{t(s)} = \frac{t(*)}{123}.$$

In fact, for a generic $\hat{p}(*)$, the estimated $\mathrm{se}\left[\hat{p}(*)\right]$, according to the ratio estimation theory, are

$$\begin{aligned}
\mathrm{se}\left[\hat{p}(*)\right] &= \frac{N}{t(P)}\sqrt{\frac{N-n}{nN}}\sqrt{s^2(*)+\hat{p}^2(*)s^2(\hat{p})-2\hat{p}(*)\mathrm{cov}(*,\hat{p})} \\
&= \frac{20}{2870}0.074536\sqrt{s^2(*)+\hat{p}^2(*)s^2(\hat{p})-2\hat{p}(*)\mathrm{cov}(*,\hat{p})} \\
&= \frac{0.074536}{143.5}\sqrt{s^2(*)+\hat{p}^2(*)s^2(\hat{p})-2\hat{p}(*)\mathrm{cov}(*,\hat{p})} \\
&= 0.000519\sqrt{s^2(*)+\hat{p}^2(*)s^2(\hat{p})-2\hat{p}(*)\mathrm{cov}(*,\hat{p})}\,.
\end{aligned}$$

The 95% confidence intervals for the proportions are computed accordingly and appear in the 2nd column of Table 2 (Panel A).

Assuming that the behavior of all 20 GPs in San Giovanni in Persiceto, as regards the object of the study, is the same, the estimates of totals can be extended to whole population of doctors under the perspective of ratio estimation. Ratio estimators of totals need the population total, $t(P)$=2870, which is known, for adjusting the sample proportions $\hat{p}_t(*)$

$$\hat{t}_{rt}(*) = \frac{t(*)}{t(p)} t(P) = t(*) \frac{2870}{2607} = \hat{p}_t(*) 2870 = t(*)\ 1.1 .$$

A similar computation is performed for the ratio estimator of the total of confirmed diagnoses among suspected, CR_2, and of the total of refusing patients among suspected, RR_r, in this case via an approximation, since the population total $t(S)$ isn't available and can only be estimated, again by a ratio estimator since n=18 is a random result, as

$$\hat{t}(s) = t(s) \frac{N}{n} = t(s)\ 1.\overline{1}$$

leading to

$$\hat{t}_{rs}(*) \simeq \frac{t(*)}{t(s)} \hat{t}(s) = \hat{p}_s(*) t(s) \frac{N}{n} = t(*)\ \frac{N}{n} = t(*)\ 1.\overline{1}.$$

Note that the adjusting factor related to patients 2870/2607=1.1 is almost equal to the adjusting factor $N / n = 1.\overline{1}$ for GPs.

The estimated standard errors for the ratio totals estimators are linear transformations of the estimated standard errors for proportions as follows

$$\mathrm{se}\left[\hat{t}_r(*)\right] = N \sqrt{\frac{N-n}{nN}} \sqrt{s^2(*) + \hat{p}^2(*) s^2(\hat{p}) - 2\hat{p}(*) \mathrm{cov}(*, \hat{p})}$$

$$= 1.490712 \sqrt{s^2(*) + \hat{p}^2(*) s^2(\hat{p}) - 2\hat{p}(*) \mathrm{cov}(*, \hat{p})}$$

and the confidence intervals follow.

Table 1. Selected sample statistics for 18 collaborating doctors in San Giovanni in Persiceto.

Sample statistics	Elderly patients $t(p)$	$t(s)$	SR	$t(prot)$	$ProtR$	$t(c)$	CR_1	$t(c)_+$ $t(prot)$	$t(r)$	$Prev$	CR_2	RR
$s(\bullet)$	49.36	4.134	0.0314	1.474	0.0114	2.975	0.0191	3.053	0.856	0.0173	0.2821	0.0930
$s(\bullet)$ <150pts	21.16	3.891	0.0239	1.506	0.0079	2.588	0.0142	3.059	0.756	0.0168	0.1987	0.0714
$s(\bullet)$ ≥150pts	36.17	4.007	0.0372	1.476	0.0135	2.914	0.0225	2.394	0.966	0.0187	0.3269	0.1103
$c(\bullet, \hat{p})$	2436.97	55.088	-0.6276	14.245	-0.2518	65.323	0.2127	79.569	-4.373	-0.0391	7.4305	-1.4446
$c(\bullet, \hat{p})$ <150pts	447.64	-49.2860	-0.3386	7.964	0.0088	-17.321	-0.1320	-9.357	-0.571	-0.1232	-0.0329	0.1179
$c(\bullet, \hat{p})$ ≥150pts	1308.06	27.944	-0.6185	-1.222	-0.2610	42.444	0.2434	41.222	-4.000	-0.0175	0.2904	0.1797
$b_{Rt}(\bullet, t(p))$	1.0000	0.0226	-0.0003	0.006	-0.0001	0.027	0.0001	0.033	-0.002	-1.6E-05	0.0030	-0.0006
$b_{Rt}(\bullet, t(p))$ >150pts	1.0000	-0.1101	-0.0008	0.018	0.0000	-0.039	-0.0003	-0.021	-0.001	-0.0003	-0.0022	0.0078
$b_{Rt}(\bullet, t(p))$ ≥150pts	1.0000	0.0214	-0.0005	-0.001	-0.0002	0.032	0.0002	0.032	-0.003	-1.3E-05	0.0181	0.0112

The symbol • denotes totals or proportions in the columns.
Covariances and regression coefficients quantify the strength of the relation between the total elderly patients t(p) and each single column in Table 1, except for CR_2 and RR columns . the regression coefficients associated to CR_2 and RR are evaluated w.r.t the suspected patients $t(s)$ instead the total elderly patients $t(p)$.

Table 2. Estimates of the relevant quantities for all GPs in San Giovanni in Persiceto under different hypotheses

PANEL A. Estimates for proportions

Group of patients	Ratio estimation	Regression estimation
Estimates for proportions $\hat{p}(*)$		
$\hat{p}_t(s) = SR$	0.04718 (0.04475 ; 0.04961)	0.04752 (0.04749 ; 0.04550)
$\hat{p}_t(prot) = ProtR$	0.01419 (0.01346 ; 0.01493)	0.01433 (0.01432 ; 0.01434)
$\hat{p}_t(c) = CR_1$	0.02417 (0.02293 ; 0.02540)	0.02405 (0.24003 ; 0.24070)
$\hat{p}_t(prev) = Prev$	0.03860 (0.03639 ; 0.04033)	0.38380 (0.38360 ; 0.38400)
$\hat{p}_s(c) = CR_2$	0.51220 (0.48608 ; 0.53831)	0.50722 (0.50115 ; 0.51329)
$\hat{p}_s(r) = RR$	0.08130 (0.07710 ; 0.08550)	0.08165 (0.07970 ; 0.08360)
PANEL B. Estimates for totals		
Estimates for totals $\hat{t}(*)$		
$\hat{t}_t(p)$	2870 [1]	2870 [1]
$\hat{t}_t(s)$	135.41 (128.43 ; 142.39)	135.34 (135.26 ; 135.43)
$\hat{t}_t(prot)$	40.73 (38.63 ; 42.84)	40.71 (40.68 ; 40.74)
$\hat{t}_t(c)$	69.36 (65.81 ; 72.90)	69.38 (69.32 ; 69.43)
$\hat{t}_t(prot) + \hat{t}_t(c)$	110.09 (104.44 ; 115.74)	110.08 (110.03 ; 110.14)
$\hat{t}_s(c)$	69.36 (63.17 ; 75.54)	69.36 (68.54 ; 70.18)
$\hat{t}_s(r)$	11.01 (10.06 ; 11.96)	11.00 (10.73 ; 11.26)

[1] values reported in AUSL data archives
In practice the values to consider will be integers.

The standard errors of $\hat{t}_{rs}(*)$ also come from ratio-type variance estimators. We compute them in the same way as $\mathrm{se}\left[\hat{t}_r(*)\right]$, without considering the further element of randomness due to the fact that an estimate appears at the place of the population value $t(S)$.

The estimates of totals with their 95% confidence intervals appear in the 2nd column of Table 2 (Panel B).

The refusal of some doctors to participate in the pilot study imposes to consider ratio-type estimators instead of direct estimators, with the consequence that all estimators are biased and their variances are

approximated and not exact. However, the high size of the sample of doctors with respect to the population (18 out of 20) allows us to consider estimates almost unbiased and their variances as almost exact. This allows us to see the estimates of Table 2 as approximately unbiased and their estimated confidence intervals as approximately exact.

Some descriptive analyses of the ELISA pilot study have been performed in order to highlight possible differences among doctors and to propose further alternative estimators in addition to the simplest version of the ratio estimator.

In the sample of 18 GPs from San Giovanni in Persiceto we found moderate negative correlation for a) the number of elderly patients and the proportion of patients with suspicion of AS (Pearson's R^2=0.164; p=0.097), while weak positive relationship was found between b) the number of elderly patients and patients with confirmed diagnosis of AS (Pearson's R^2=0.198; p=0.064) as well as between c) the number of elderly patients and the prevalence of AS (Pearson's R^2=0.279; p=0.024). The relationship between the number of elderly patients and the number of suspected patients was further examinated for the subgroups of doctors with less and more than 150 elderly patients:

(1) while for the whole sample of 18 GPs the correlation was slight negative (as mentioned above), for the subgroups of GPs with ≥150elderly patients this relationship was more evident (R^2=0.446, p=0.070) in comparison with the subgroup of GPs with <150 elderly patients (R^2=0.211, p=0.182);

(2) for the GPs with less than 150 elderly patients the relationship between the number of elderly patients and proportion of patients with confirmed AS diagnosis from elderly patients was slightly positive (R^2=0.089, p=0.401), while for the GPs with more than 150 patients it was slightly negative (R^2=0.193, p=0.277).

Such evidences make us conjecture that GPs with a lower number of elderly patients might tend to identify a higher fraction of patients suspected of AS diagnosis, sending them to further examination (points a) and b) above). In addition, from point c) we might assume that GPs with a lower number of elderly patients than 150 tend to identify a higher fraction of suspected rather than the GPs with more than 150 elderly people. At the same time, according to Table 1, GPs with lower than 150 elderly patients seem to be less reliable than their colleagues with more

than 150 elderly patients (see in Table 1 the regression coefficients as regards CR_1 and CR_2 values for the two classes. Grouping the 18 volunteers according to their specialization doesn't help: only 3 GPs possess a specialization in cardiology or geriatrics. No characteristic of the GPs can be directly associated with the number of confirmed AS diagnosis.

The only potential categorization parameter giving us guidance by assessment of GPs' work is the total number of elderly patients.

Splitting the set of doctors into 2 groups: with <150 and with ≥150 elderly patients shows different trends in doctors' behavior. In particular, covariances with opposite sign for these two sub-groups are detected. This doesn't support the proposal of different ratio estimators, which need to compute always positive ratios: positive ratios, when multiplied by the covariances for constructing the variance of estimators, wouldn't lead to a reduction of the variance with respect to the consideration of the whole sample.

A way for keeping into account individual characteristics considers sample covariances that are the basis for the regression coefficients estimators calculated as

$$b_{Rt}\left(t(*),t(p)\right)=\frac{c(t(*),t(p))}{v^2\left(t(p)\right)}$$

and

$$b_{Rs}\left(t(*),t(s)\right)=\frac{c(t(*),t(s))}{v^2\left(t(s)\right)}$$

which allow to compute the regression estimators of the proportions as

$$\hat{p}_{Rt}(*)=\hat{p}_t(*)+b_{Rt}\left(t(*),t(p)\right)\left(m(P)-\hat{p}_t(p)\right)$$

and

$$\hat{p}_{Rs}(*)=\hat{p}_s(*)+b_{Rs}\left(t(*),t(s)\right)\left(\hat{m}_{rs}(s)-\hat{p}_s(s)\right),$$

where

$$\hat{m}_{rs}(s)=\frac{\hat{t}_{rs}(s)}{N}$$

and of the totals as

$$\hat{t}_{Rt}(*)=\hat{t}_{rt}(*)+b_{Rt}\left(t(*),t(p)\right)\left(t(P)-\hat{t}_{rt}(p)\right)$$

$$\hat{t}_{Rs}(*) = \hat{t}_{ns}(*) + b_{Rs}\left(t(*), t(s)\right)\left(\hat{t}_{ns}(s) - \hat{t}_{ns}(s)\right)$$

where approximated unbiased ratio estimators are used instead of the exactly unbiased estimators.

The estimated standard errors of the 4 quantities above follow a common scheme, here illustrated for $\hat{t}_{Rt}(*)$:

$$\mathrm{se}\left[\hat{t}_{Rt}(*)\right] = N\sqrt{\frac{N-n}{nN}}\sqrt{s^2(*) + b_{Rt}^2\left(t(*), t(p)\right)s^2(\hat{p}) - 2b_{Rt}\left(t(*), t(p)\right)\mathrm{cov}\left(t(*), \hat{p}\right)}$$

and their 95% CIs are computed accordingly.

The results on regression estimates appear in the 3rd column of Table 2. Their estimated confidence intervals are much narrower than the confidence intervals of ratio estimates. Being approximated, they are over optimistic, but produce a conclusion that is a promising suggestion for analyzing the results of the future sample.

5. The sampling plan for the city of Bologna

The pilot study of San Giovanni in Persiceto constituted an appropriate guidance for constructing a sample of doctors, with the important conclusion that the number of elderly patients was found very important, since a number of the sample parameters are different for the groups of doctors defined according to the total number of their elderly patients. For GPs with higher number of patients, also the risk of errors and ineffectiveness in work with medical records might be higher. Our main concern for the future sampling plan is trying to avoid a less careful behavior of GPs with many patients with respect to the other group. The prevalence of AS on the area of the Bologna city cannot be estimated without a well-designed probabilistic sampling plan of GPs.

Since the assessment of AS prevalence is conditional on identifying suspected cases, a careful random sampling design is needed for a large population like the one of the city of Bologna, in order to estimate the number of patients with a suspicion of AS which will be further examined in the hospitals. In the Italian region health-care system, the

population of patients is hierarchically clustered in the population of their GPs, seen as complex units. The Emilia-Romagna experience of the NCP classification as an administrative and professional grouping is fundamental for the construction of the sample. Moreover, the variance in number of elderly patients within Bologna city is higher than in San Giovanni in Persiceto (values computed on AUSL dataset): the average number of elderly patients per doctor in Bologna is 198 with variance 5857 while the average number of elderly patients for the 20 doctors from San Giovanni in Persiceto is 165.5 with variance 3055. This would result in larger confidence intervals and lower reliability of the estimates for the city of Bologna without a suitable sampling plan.

The construction of a reliable sample is very important: the size of the sample of suspected AS patients has to be maintained within reasonable limits for not causing too high burden for cardiologists. The precautionary total number of 300-350 elderly patients for ECO examination is the feasible amount sustainable by the ELISA researchers: this value is a benchmark for the sampling design. The estimate of suspected AS patients in the population will be the primary task of the survey, then the set of quantities illustrated in Section 4 for the pilot study will be the further important object of estimation.

Considering all information and results from the pilot study and the general characteristics of the GPs population, the final sample of doctors is defined after several steps. As physicians with a low number of old patients (less than 50) constitute a sub-group corresponding to a very small sub-population of patients (from Table A3, 2nd column: 1257 patients; 1.1% within the whole AUSL territory of Bologna; 0.9% within the city), they were excluded from the sample. By observing the population distribution within the AUSL territory, the decision of restricting in this way the target population for the city of Bologna was taken. The selected subpopulation of doctors and their patients is reported in Table A9. The sampling plan is tailored according to the characteristics of the city of Bologna, which appears to be much older than the rest of the AUSL territory. The sampling plan aims at asking GPs to screen an acceptable number of patients. Table A9 (Panel C) points out that most doctors have a high average number of patients that is difficult to screen properly. The conjecture about different behavior of doctors with high number of patients suggests an important restriction in the organization of the population to screen, shown in Figure 3.

A sample of the 80 doctors with less than 150 elderly patients will be asked to screen the whole group (syntheses of this set of doctors and their patients are described in the 2nd column of Table A9) while the sampled doctors with more patients will screen from smaller populations of elderly patients falling in pre-defined age classes. This grouping consists in the stratification of doctors, which is planned by the investigators and induces a controlled variability in results. In the last two tables, namely Table A10 and Table A11, we split the 186 GPs with more than 150 elderly patients in two groups, respectively of 96 and 90 members, each related to a distinct sub-population 1) the population of patients in age 75-80 years (Table A10); 2) the population of patients in age 81-95 years (Table A11). A detailed description of sub-groups of doctors and their patients according to their age is reported in the two tables. The complementary sub-populations of 12.293 patients in age 81-95 years of the first 96 doctors and of 9.452 patients in age 75-80 years of the second group of 90 doctors is excluded from sampling. The prevalence of the disease for these sub-populations has to be estimated on the basis of the sample which will be collected.

Following the above steps we construct 54 homogenous clusters of practitioners (2nd column in Table A9, and Tables A10 and A11). Investigators will randomly choose one doctor from each cluster. This means that the GPs of the first 6 clusters are selected from Panel A of Table A9. Tables A10 and A11 report the number of doctors in each of the 24 clusters constructed according to the number of old patients in the two sub-populations: one doctor will be selected from each cluster. The total number of patients screened by their GPs will be known only after the sampling selection and will be non-random.

In conclusion, the average number of patients per doctor in the 6 clusters of GPs with 50 to 149 old patients is 107.1 (see Panel C of Table A9). The corresponding values for the doctors with more patients appear in Panel C of Tables A10 and A11, where the average number of patients per doctor to screen is respectively 108.8 in the sub-population of patients until 80 years and 132.6 in the sub-population of patients over 81 years.

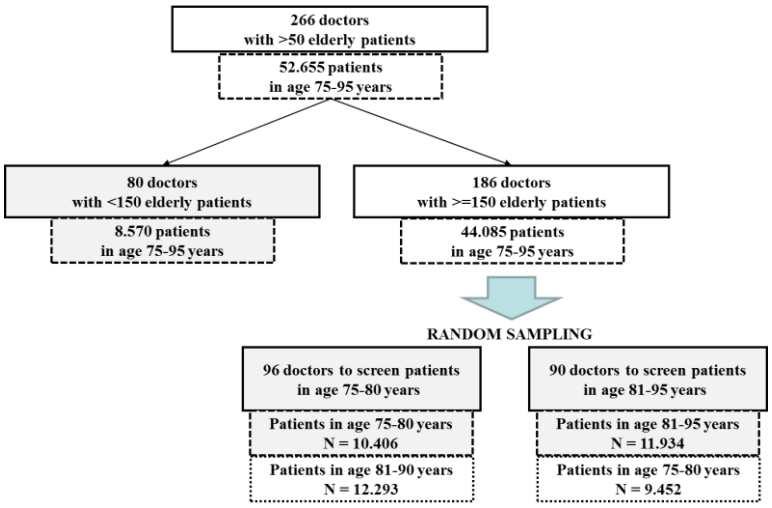

Figure 3. Identification of the population to sample

A rough estimate of the total number of patients to screen is therefore 6500, that is the sum of the averages of elderly (resp. young- and old-elderly) patients through the whole set of 54 clusters (the 2nd column of Panel C in table A9 and all elements of Panel C in both Tables A10 and A11). Since the proportion of suspected patients evaluated in the pilot study is 0.0472 with 95% confidence limits (0.0448; 0.0496), the rough ex ante estimate of patients to send to further examination is 307 with 95% confidence limits (291; 323).

The above considerations illustrate how the results on ratio estimators, with higher estimated approximated confidence intervals, are the basis for the rough estimate of the anticipated final number of suspected since they produce conservative results. For suitably computing all estimates, the number of patients that refuse to participate in the study and the number of patients that refuse to undertake the ECO examination have to be collected. We stress that the planned size of the sample of GPs, n=54, is a non- random value. The planned design which invites sampled doctors to examine a pre-fixed sub-set of patients will avoid uncontrolled randomness in the final syntheses which might be induced by the behavior of GPs. After the selection of GPs also the number of their patient will be known in advance. The sampling plan for Bologna is conceived in order to avoid obtaining means and proportions with

random denominators. For the sample results of Bologna it will be possible to use the simplest direct estimates of finite population inference as sample proportions and expansion estimators for the totals that weren't allowed for the sampling results of San Giovanni in Persiceto. Regression type corrections will be applied as a second step, in order to obtain estimates with a reduced variance, in analogy to what has already been noticed in the pilot study. In this way, the unexpected randomness of the results remarked in the pilot study, which requested the use of ratio-type estimates, won't be present.

6. Conclusions

In this paper we start from the results of a pilot study on the prevalence estimation of AS in the elderly population in the municipality of San Giovanni in Persiceto and strengthen inference on that municipality using the information on patients' and GPs' database provided on the whole territory of the AUSL. The availability of the AUSL health-care system population data-base for the municipality of Bologna revealed as a general powerful tool for planning a sampling design able to reach the elderly population via their GPs. We propose a sampling plan of GPs that can be the basis for any other epidemiological study.

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Appendix

'Zone'	'NCP-unit'
Borgo – Panigale	Borgo – Panigale
Navile	Navile 1
	Navile 2
	Navile 3
San Donato – San Vitale	San Donato 1
	San Donato 2
	San Vitale 1
	San Vitale 2
Saragozza - Porto	Saragozza
	Porto 1
	Porto 2
Savena - Santo Stefano	Savena 1
	Savena 2
	Savena 3
	Santo Stefano 1
	Santo Stefano 2

Figure A1. Partition of the AUSL district 'Città di Bologna' into 'zones', and 'NCP-units' (Nuclei di Cure Primarie)

Table A1. Basic clinical and psychological characteristics of patients with confirmed and not approved diagnosis of AS by ECO

Panel A – Basal clinical characteristics

	All patients[#]	**Confirmed AS**	**Disproved AS**
N	**113**	**63**	**50**
Age [mean±SD]	81.4±4.3	81.6±4.2	81.1±4.6
Females [n(%)]	71 /62.8%	40 /63.5%	31 /62%
PAD [n(%)]	6 /5.3%	3 /4.8%	3 /6%
COPD grade moderate/severe [n(%)]	5 /4.4%	3 /4.7%	2 /4%
Robust physical construction [n(%)]	49 /43.4%	28 /44.4%	21 /42%
NYHA class III-IV [n(%)][*]	9 /8%	7 /11.1%	2 /4%
Dyspnea [n(%)]	33 /29.2%	23 /36.5%	10 /20%
Syncope [n(%)]	5 /4.4%	3 /4.8%	2 /4%
Angina pectoris [n(%)]	6 /5.3%	6 /9.5%	0 /0%
DM [n(%)]	21 /18.6%	14 /22.2%	7 /14%
Transaortic gradient [n(%)]	113 /100%	63 /100%	50 /100%
Grad max <10mmHg [n(%)]	14 /12.4%	0 /0%	14 /28%
Grad max 10-19mmHg [n(%)]	36 /31.9%	0 /0%	36 /72%
Grad max 20-39mmHg [n(%)]	35 /31%	35 /55.6%	0 /0%
Grad max 40-59mmHg [n(%)]	13 /11.5%	13 /20.6%	0 /0%
Grad max ≥60mmHg [n(%)]	15 /13.3%	15 /23.8%	0 /0%
Grad max [mean]	28.5	41.6	10.4
Ao Reg (moderate - severe grade) [n(%)]	3 /2.7%	2 /3.2%	1 /2%
Mi Reg (moderate - severe grade) [n(%)][*]	10 /8.8%	4 /6.3%	6 /12%
Neoplasm [n(%)]	17 /15%	13 /20.6%	4 /8%

Table A1-continued. Basic clinical and psychological characteristics of patients with confirmed and not approved diagnosis of AS by ECO

Panel B – Psychological characteristic of interviewed patients

	All patients[#]	**Confirmed AS**	**Disproved AS**
EuroQoL [N]	73	55	18
Total score [mean]	0.68	0.67	0.72
VAS [N]	73	55	18
VAS [mean]	68.6	67.2	72.8
HADS [N]	71	54	17
Anxiety [n(%)][**]	9 /12.7%	6 /11.1%	3 /17.6%
Depression [n(%)]	13 /18.3%	10 /18.5%	3 /17.6%
SPMSQ [N]	73	54	19
Cognition impairment: moderate-severe grade [n(%)]	8 /11.0%	3 /5.6%	5 /26.7%

[**] $p<0.001$; [*] $p<0.050$ (Chi-square test/Fisher test/Man-Whitney U test for testing differences between groups with confirmed AS or disproved AS); EuroQoL – general health status questionnaire; HADS – Anxiety and depression score; SPMSQ – mental status questionnaire

[#] clinical characteristics only for patients with ECO examination; patients with prothesis are not included

Percent proportions are calculated within each group. For the HADS and SPMSQ questionnaire it was calculated from the interviewed sub-population of patients.

Table A2. Odds ratio of selected clinical and psychological characteristics for patients with confirmed AS diagnosis within the group of 113 patients undertaking ecocardiographical examination

Clinical parameters	**Wald test P**	**OR (95% CI)**
Presence of dyspnea	0.051	2.36 (0.99:5.59)
Neoplasm	0.057	3.18 (0.97;10.48)
Presence of mitral regurgitation	0.105	0.31 (0.08:1.28)
NYHA class III-IV	0.178	3.05 (0.61:15.39)
Previous DM	0.219	1.87 (0.69:5.07)
Robust physical construction	0.790	1.11 (0.51:2.41)

Table A3. Doctors and elderly patients in the territory of AUSL Bologna (geographical division into areas and districts)

Panel A. Classification of GPs in clusters constructed according to the geographical area and the number of elderly patients per doctor

Number of elderly patients (categories)	**0 – 49 pts**	**50 – 99 pts**	**100 – 149 pts**	**150 – 199 pts**	**200 – 249 pts**	**250 - 299 pts**	**300 - 399 pts**	**Total**
Number of GPs								
Area (district)	**46**	**72**	**120**	**137**	**144**	**68**	**30**	**617**
Area – CITTÀ	17	31	49	54	54	52	26	283
CITTÀ DI BOLOGNA	17	31	49	54	54	52	26	283
Area – SUD	15	27	44	45	38	8	3	180
CASALECCHIO RENO	7	10	20	19	18	4	2	80
PORRETTA TERME	3	8	6	13	12	2	0	44
SAN LAZZARO	5	9	18	13	8	2	1	56
Area – NORD	14	14	27	38	52	8	1	154
PIANURA EST	11	6	14	21	39	6	1	98
PIANURA OVEST	3	8	13	17	13	2	0	56
S. Giovanni (ELISA 20GPs)	*1*	*2*	*4*	*7*	*5*	*1*	*0*	*20*

Panel B. Classification of elderly patients in age 75 -95 in clusters constructed according to the geographical area and the number of elderly patients per doctor

Sum of elderly patients								
Area (district)	**1257**	**5505**	**15301**	**23845**	**32140**	**18323**	**9766**	**106137**
Area – CITTÀ	477	2320	6250	9381	12110	14081	8513	53132
CITTÀ DI BOLOGNA	477	2320	6250	9381	12110	14081	8513	53132
Area – SUD	391	2133	5667	7938	8545	2104	945	27723
CASALECCHIO RENO	209	803	2542	3340	4071	1026	608	12599
PORRETTA TERME	21	619	779	2263	2724	556	0	6962
SAN LAZZARO	161	711	2346	2335	1750	522	337	8162
Area – NORD	389	1052	3384	6526	11485	2138	308	25282
PIANURA EST	282	441	1769	3540	8683	1587	308	16610
PIANURA OVEST	107	611	1615	2986	2802	551	0	8672
S. Giovanni (ELISA 20GPs)	*47*	*176*	*506*	*1242*	*1078*	*261*	*0*	*3310*

Table A3-continued. Doctors and elderly patients in the territory of AUSL Bologna (geographical division into areas and districts)

Panel C. Percent proportion of elderly patients from all patients per doctor (mean, min-max) in clusters constructed according to the geographical area and the number of elderly patients per doctor

% of elderly patients(mean, min-max)	**0 – 49 pts**	**50 – 99 pts**	**100 – 149 pts**	**150 – 199 pts**	**200 – 249 pts**	**250 - 299 pts**	**300 - 399 pts**	**Total**
All districts	**8.3 (0.1;20.0)**	**10.8 (4.6;25.6)**	**12.3 (6.6;36.0)**	**13.4 (9.0; 21.9)**	**15.6 (11.5;27.3)**	**17.9 (14.6;24.9)**	**20.3 (16.9;26.1)**	**13.8 (0.1;36.0)**
Area – CITTÀ	8.7 (1.6;15.4)	11.2 (6.4;17.5)	12.8 (6.6;20.9)	14.3 (9.0;21.0)	16.6 (12.7;27.3)	18.1 (14.6;24.9)	20.2 (16.9;24.8)	15.0 (1.6;27.3)
CITTÀ DI BOLOGNA	8.7 (1.6;15.4)	11.2 (6.4;17.5)	12.8 (6.6;20.9)	14.3 (9.0;21.0)	16.6 (12.7;27.3)	18.1 (14.6;24.9)	20.2 (16.9;24.8)	15.0 (1.6;27.3)
Area – SUD	8.4 (2.0;15.1)	11.7 (6.8;25.6)	12.8 (6.9;36.0)	13.4 (9.4;21.9)	15.3 (12.2;18.9)	17.7 (15.0;19.4)	21.7 (17.9;26.1)	13.3 (2.0;36.0)
CASALECCHIO RENO	7.4 (3.8;13.4)	11.4 (6.9;18.8)	11.8 (6.9;20.5)	13.5 (9.4;21.3)	15.2 (12.5;18.1)	16.9 (15.0;19.1)	19.5 (17.9;21.2)	12.9 (3.8;21.3)
PORRETTA TERME	9.9 (2.0;15.1)	13.0 (7.7;25.6)	17.5 (10.1;36.0)	13.7 (10.0;21.9)	16.0 (12.2;18.9)	18.6 (18.5;18.7)	- (-; -)	14.7 (2.0;36.0)
SAN LAZZARO	8.8 (4.6;12.0)	10.8 (6.8;17.7)	12.4 (7.4;19.8)	13.0 (9.5;17.7)	14.8 (13.3;18.2)	18.2 (17.1;19.4)	26.1 (26.1;26.1)	12.7 (4.6;26.1)
Area – NORD	7.7 (0.1;20.0)	8.4 (4.6;16.8)	10.7 (6.9;14.5)	12.2 (9.1;18.7)	14.7 (11.5;20.7)	17.1 (15.9;18.3)	18.8 (18.8;18.8)	12.3 (0.1;20.7)
PIANURA EST	7.1 (0.1;20.0)	7.1 (4.6;8.7)	10.6 (6.9;14.5)	11.6 (9.1;18.7)	14.7 (11.5;20.7)	17.0 (15.9;17.9)	18.8 (18.8;18.8)	12.3 (0.1;20.7)
PIANURA OVEST	9.4 (6.2;12.8)	9.4 (5.1;16.8)	10.8 (7.7;14.5)	12.9 (9.6;16.8)	14.8 (12.3;17.1)	17.4 (16.6;18.3)	- (-; -)	12.3 (5.1;18.3)
S. Giovanni (ELISA 20GPs)	9.3 (9.3;9.3)	10.8 (9.3;12.4)	11.7 (10.6;12.8)	14.1 (12.0;16.8)	15.4 (14.7;15.8)	16.6 (16.6;16.6)	- (-; -)	13.7 (9.3;16.8)

Table A4. Classification of doctors and their patients according to the specialization of the physicians within the NPC classification in the city of Bologna

NCP unit	Doctors	N of doctors with specialization in cardiology and geriatry	Elderly patients	Elderly patients of doctors with specialization in cardiology and geriatry
	N	N / %	N	N / %
BOLOGNA [#]	**266**	**67/ 25.2%**	**52 655**	**14 614/ 27.8%**
BORGO PANIGALE	15	3/ 20%	3013	773/ 25.7%
NAVILE 1	14	3/ 28.6%	3074	986/ 32.1%
NAVILE 2	12	0/ 0%	2256	0/0%
NAVILE 3	17	3/ 17.6%	3103	751/ 24.2%
PORTO 1	11	3/ 27.3%	2494	756/ 30.3%
PORTO 2	21	5/ 23.8%	3721	753/ 20.2%
RENO 1	12	3/ 25%	2276	697/ 30.6%
RENO 2	14	4/ 28.6%	3180	914/ 28.7%
S. DONATO 1	11	2/ 18.2%	2054	390/ 19%
S. DONATO 2	12	2/ 16.7%	2239	372/ 16.6%
S. STEFANO 1	17	6/ 35.3%	3067	1324/ 43.2%
S. STEFANO 2 [#]	15	6/ 40%	2900	1504/ 51.9%
S. VITALE 1	17	4/ 23.5%	3062	844/ 27.6%
S. VITALE 2	16	3/ 18.8%	2631	580/ 22%
SARAGOZZA	18	6/ 33.3%	3820	1477/ 38.7%
SAVENA 1	15	6/ 40%	3334	1185/ 35.5%
SAVENA 2 [#]	14	3/ 21.4%	3009	466/ 15.5%
SAVENA 3	15	4/ 26.7%	3422	842/ 24.6%

[#] statistically significant difference ($p<0.050$, Mann-Whitney U test) in total number of patients and proportion of elderly patients between GPs groups with and without target specialization

Percentages are calculated within each NCP unit.

Table A5. Classification of doctors and their patients according to the length of praxis of physician within the NPC classification in the city of Bologna

NCP unit	N of doctors	N of all elderly patiens	N of doctors according to their lenght of praxis <20yrs/21-30yrs/ >=31yrs	% of all elderly patiens redards the legth of praxis <20yrs/21-30yrs/ >=31yrs
City of Bologna	**266**	**52 655**	**19/ 122/ 125**	**6.5/ 47.6/ 45.9**
BORGO PANIGALE	15	3013	0/ 11/ 4	0/ 77.6/ 22.4
NAVILE 1	14	3074	3/ 9/ 2	20/ 64.5/ 15.5
NAVILE 2	12	2256	2/ 1/ 9	23.7/ 5.6/ 70.7
NAVILE 3	17	3103	0/ 6/ 11	0/ 40/ 60
PORTO 1	11	2494	0/ 4/ 7	0/ 34.7/ 65.3
PORTO 2	21	3721	2/ 8/ 11	6.4/ 36.5/ 57.1
RENO 1	12	2276	0/ 5/ 7	0/ 48.3/ 51.7
RENO 2	14	3180	2/ 9/ 3	12.3/ 72.2/ 15.5
S. DONATO 1	11	2054	1/ 5/ 5	7.2/ 51.9/ 40.9
S. DONATO 2	12	2239	0/ 5/ 7	0/ 50.5/ 49.5
S. STEFANO 1	17	3067	1/ 8/ 8	8/ 51.1/ 40.9
S. STEFANO 2	15	2900	2/ 1/ 12	4.7/ 8/ 87.3
S. VITALE 1	17	3062	1/ 10/ 6	4.3/ 55.9/ 39.7
S. VITALE 2	16	2631	0/ 7/ 9	0/ 41.8/ 58.2
SARAGOZZA	18	3820	3/ 7/ 8	15.9/ 39.6/ 44.5
SAVENA 1	15	3334	1/ 6/ 8	2.3/ 38.9/ 58.7
SAVENA 2	14	3009	1/ 7/ 6	9/ 41.4/ 49.6
SAVENA 3	15	3422	0/ 13/ 2	0/ 84.6/ 15.4

Length of praxis is defined as time from date of graduation until the 31st December 2009. Percentages are calculated within each NCP unit.

Table A6. Population in the Bologna AUSL territory according to the data source

Population	Demographic data	AUSL data	Difference (demographic – AUSL)
Total	853.320	838.378	+14.942
Male	410.001	399.506	+10.495
Female	443.319	438.872	+4.447

AUSL Bologna (updated data for 31st December 2009). Demographic data corresponding to the population administrative summaries of year 2009 (www.provincia.bologna.it) without the municipalities of the 'circondario di Imola'.

Table A7. Population in age 75-95 within the city of Bologna

Panel A. Total elderly population in the districts of Bologna

District of Bologna	Demographic data N	AUSL data N	Difference (demographic – AUSL) N	%
Bologna	52835	52655	+180	+0.3
Borgo Panigale - Reno	8388	8469	-81	-1.0
Navile	8247	8433	-186	-2.3
San Donato - San Vitale	10304	9986	+318	+3.1
Saragozza - Porto	9682	10035	-353	-3.6
Savena - Santo Stefano	16214	15732	+482	+3.0
Panel B. Elderly men in the districts of Bologna				
Bologna	18990	19415	-425	-2.2
Borgo Panigale - Reno	3197	3271	-74	-2.3
Navile	8247	8433	-186	-2.3
San Donato - San Vitale	3581	3578	+3	-0.1
Saragozza - Porto	3274	3546	-272	-8.3
Savena - Santo Stefano	5947	5913	+34	-0.6
Panel C. Elderly women in the districts of Bologna				
Bologna	33845	33240	+605	+1.8
Borgo Panigale - Reno	5191	5198	-7	-0.1
Navile	8247	8433	-186	-2.3
San Donato - San Vitale	6723	6408	+315	+4.7
Saragozza - Porto	6408	6489	-81	-1.3
Savena - Santo Stefano	10267	9819	+448	+4.4

Sources: www.iperbole.bologna.it (data for year 2009), AUSL dataset (updated data at 31st December 2009)

Table A8. Summaries of the elderly population in San Giovanni in Persiceto, sample of n=18 doctors

	POPULATION DATA		SAMPLING DATA										
Doctors	**All patients**[a]	**Elderly patients**[b] ***t(p)***	***t(s)***	***SR***	***t(prot)***	***ProtR***	***t(c)***	***CR_1***	***CR_2***	***t(r)***	***RR***	***$t(c)_+$ t(prot)***	***Prev***
Doctor 1 [3]	1 598	183	12	0.0655738	0	0	8	0.043716	0.666667	0	0	8	0.043716
Doctor 2	1 565	65	4	0.061539	2	0.030769	0	0	0	0	0	2	0.030769
Doctor 3 [1, 2, 3]	1 550	197	11	0.055838	5	0.025381	8	0.040609	0.727273	2	0.181818	13	0.065990
Doctor 4	1 400	127	0	0	4	0.031496	0	0	0	0	0	4	0.031496
Doctor 5 [2, 3]	1 323	175	6	0.034286	1	0.005714	4	0.022857	0.666667	0	0	5	0.028571
Doctor 6	1 349	101	12	0.118812	1	0.009901	5	0.049505	0.416667	3	0.250000	6	0.059406
Doctor 7 [1, 3]	1 271	189	8	0.042328	2	0.010582	6	0.031746	0.750000	1	0.125000	8	0.042328
Doctor 8 [1]	1 167	132	4	0.030303	2	0.015152	3	0.022727	0.750000	0	0	5	0.037879
Doctor 9 [2, 3]	1 099	189	6	0.031746	2	0.010582	1	0.005291	0.166667	0	0	3	0.015873
Doctor 10	1 079	137	6	0.043796	4	0.029197	0	0	0	1	0.166667	4	0.029197
Doctor 11	1 027	40	4	0.100000	1	0.025000	0	0	0	1	0.250000	1	0.025000
Doctor 12 [3]	887	233	3	0.012876	3	0.012876	2	0.008584	0.666667	0	0	5	0.021459
Doctor 13 [2]	851	147	13	0.088435	0	0	9	0.061225	0.692308	1	0.076923	9	0.061225
Doctor 14 [2]	772	86	4	0.046512	3	0.034884	3	0.034884	0.750000	0	0	6	0.069767
Doctor 15 [3]	492	164	15	0.091463	3	0.018293	6	0.036585	0.400000	1	0.066667	9	0.054878
Doctor 16 [2, 3]	1 388	172	7	0.040698	3	0.017442	4	0.023256	0.571429	0	0	7	0.040698
Doctor 17	1 376	129	3	0.023256	1	0.007752	1	0.007752	0.333333	0	0	2	0.015504
Doctor 18	1 311	141	5	0.035461	0	0	3	0.021277	0.600000	0	0	3	0.021277
All collaborative doctors	**21505**	**2607**	**123**	**0.047181**	**37**	**0.0141926**	**63**	**0.024166**	**0.512195**	**10**	**0.081301**	**100**	**0.038358**
Doctor 19 [2, 3]	1 396	170	-	-	-	-	-	-	-	-	-	-	-
Doctor 20	962	93	-	-	-	-	-	-	-	-	-	-	-
All doctors	**23863**	**2870**											

[1] doctors with speciallization in cardiology, internal medicine or geriatrics; [2] doctors with praxis longer than 30 years ; [3] doctor with more than 150 patients; [a] data coming from ASL dataset; [b] data reported by ELISA investigators; Proportions in section ‚Sampling data' are derived from the column ‚Elederly patients'.

Table A9. Classification of doctors and patients for the survey in the city of Bologna

Panel A. Classification of GPs in clusters constructed according to zones and the number of patients (75-95 years) per doctor

Number of elderly patients - categories	**50 – 149 pts**	**150 – 179 pts**	**180 – 214 pts**	**215 – 249 pts**	**250 - 365 pts**	**Total**
Number of GPs	**80**	**54**	**42**	**43**	**47**	**266**
Zone						
BORGO PANIGALE – RENO	10	8	10	4	9	**41**
NAVILE	12	12	5	9	5	**43**
SARAGOZZA – PORTO	14	10	7	9	10	**50**
S. DONATO – S. VITALE	26	9	7	6	8	**56**
S. STEFANO	10	8	4	5	5	**32**
SAVENA	8	7	9	10	10	**44**

Panel B. Classification of elderly patients (75-95 years) in clusters constructed according to zones and the number of patients per doctor

Number of elderly patients	**8 570**	**9 381**	**9 175**	**11 004**	**14 525**	**52 655**
Zone						
BORGO PANIGALE – RENO	1084	1326	2184	1031	2844	**8 469**
NAVILE	1284	2154	1111	2301	1583	**8 433**
SARAGOZZA – PORTO	1486	1695	1500	2333	3021	**10 035**
S. DONATO – S. VITALE	2930	1565	1567	1504	2420	**9 986**
S. STEFANO	934	1421	872	1272	1468	**5 967**
SAVENA	852	1220	1941	2563	3189	**9 765**

Panel C. Average number of patients (75-95 years) per doctor (mean) in clusters constructed according to zones and the number of patients per doctor

Mean number of elderly patients per GP	**107.1**	**173.7**	**218.5**	**255.9**	**310.8**	**198.3**
Zone						
BORGO PANIGALE – RENO	108.4	165.6	218.4	257.8	312.9	**205.9**
NAVILE	107.0	179.5	222.2	255.7	312.5	**195.6**
SARAGOZZA – PORTO	106.1	169.5	214.3	259.2	315.2	**203.3**
S. DONATO – S. VITALE	112.7	173.9	223.9	250.7	307.5	**179.1**
S. STEFANO	93.4	177.6	218.0	254.4	303.2	**188.0**
SAVENA	106.5	174.3	215.7	256.3	310.2	**220.0**

Table A10. Classification of doctors with more than 150 patients and patients in age 75-80 years for the survey in the city of Bologna

Panel A. Classification of GPs in clusters constructed according to zones and the number of patients (75-80 years) per doctor

Number of elderly patients - categories	**150 – 179 pts**	**180 – 214 pts**	**215 – 249 pts**	**250 - 365 pts**	**Total**
Number of GPs	**28**	**22**	**21**	**25**	**96**
Zone					
BORGO PANIGALE–RENO	4	5	2	5	**16**
NAVILE	6	3	4	3	**16**
SARAGOZZA – PORTO	5	4	5	5	**19**
S. DONATO – S. VITALE	5	3	3	4	**15**
S. STEFANO	4	2	2	3	**11**
SAVENA	4	5	5	5	**19**

Panel B. Classification of elderly patients (75-80 years) in clusters constructed according to zones and the number of patients per doctor

Number of elderly patients	**2 200**	**2 254**	**2 437**	**3 515**	**10 406**
Zone					
BORGO PANIGALE–RENO	325	536	251	734	**1 846**
NAVILE	473	335	437	423	**1 668**
SARAGOZZA – PORTO	362	390	564	653	**1 969**
S. DONATO – S. VITALE	416	297	368	585	**1 666**
S. STEFANO	280	165	254	441	**1 140**
SAVENA	344	531	563	679	**2 117**

Panel C. Average number of patients (75-80 years) per doctor (mean) in clusters constructed according to zones and the number of patients per doctor

Mean number of elderly patients per GP	**78.6**	**102.5**	**116.1**	**142.1**	**108.8**
Zone					
BORGO PANIGALE–RENO	81.3	107.2	125.5	149.1	**116.1**
NAVILE	78.8	111.7	109.3	143.3	**104.7**
SARAGOZZA – PORTO	72.4	97.5	112.8	133.3	**104.3**
S. DONATO – S. VITALE	83.2	99.0	122.7	146.3	**111.1**
S. STEFANO	70.0	82.5	127.0	146.5	**103.5**
SAVENA	86.0	106.2	112.6	137.1	**111.8**

Table A11. Classification of doctors with more than 150 patients and patients in age 81-95 years for the survey in the city of Bologna

Panel A. Classification of GPs in clusters constructed according to zones and the number of patients (81-95 years) per doctor

Number of elderly patients - categories	**150 – 179 pts**	**180 – 214 pts**	**215 – 249 pts**	**250 - 365 pts**	**Total**
Number of GPs	**26**	**20**	**22**	**22**	**90**
Zone					
BORGO PANIGALE–RENO	4	5	2	4	**15**
NAVILE	6	2	5	2	**15**
SARAGOZZA – PORTO	5	3	4	5	**17**
S. DONATO – S. VITALE	4	4	3	4	**15**
S. STEFANO	4	2	3	2	**11**
SAVENA	3	4	5	5	**17**

Panel B. Classification of elderly patients (81-95 years) in clusters constructed according to zones and the number of patients per doctor

Number of elderly patients	**2 521**	**2 366**	**3 238**	**3 809**	**11 934**
Zone					
BORGO PANIGALE–RENO	353	553	288	692	**1 886**
NAVILE	583	251	730	358	**1 922**
SARAGOZZA – PORTO	514	356	580	870	**2 320**
S. DONATO – S. VITALE	363	477	446	639	**1 925**
S. STEFANO	437	285	472	324	**1 518**
SAVENA	271	444	722	926	**2 363**

Panel C. Average number of patients (81-95 years) per doctor (mean) in clusters constructed according to zones and the number of patients per doctor

Mean number of elderly patients per doctor	**97.0**	**118.3**	**147.2**	**173.1**	**132.6**
Zone					
BORGO PANIGALE–RENO	88.3	110.6	144.0	173.0	**125.7**
NAVILE	97.2	125.5	146.0	179.0	**128.1**
SARAGOZZA – PORTO	102.8	118.7	145.0	174.0	**136.5**
S. DONATO – S. VITALE	90.8	119.3	148.7	159.8	**128.4**
S. STEFANO	109.3	142.5	157.3	162.0	**138.0**
SAVENA	90.3	111.0	144.4	185.2	**139.0**