The Rationale/Design of the Guimarães/Vizela Study: A Multimodal Population-Based Cohort Study to Determine Global Cardiovascular Risk and Disease

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Background: Cardiovascular disease and dementia are growing medical and social problems in aging societies. Appropriate knowledge of cardiovascular disease and cognitive decline risk factors (RFs) are critical for global CVR health preventive intervention. Many epidemiological studies use case definition based on data collected/measured in a single visit, a fact that can overestimate prevalence rates and distant from clinical practice demanding criteria. Portugal displays an elevated stroke mortality rate. However, population's global CV risk characterization is limited, namely, considering traditional/nontraditional RF and new intermediate phenotypes of CV and renal disease. Association of hemodynamic variables (pulse wave velocity and central blood pressure) with global CVR stratification, cognitive performance, and kidney disease are practically inexistent at a dwelling population level.

Study Design and Methods: After reviewing published data, we designed a population-based cohort study to analyze the prevalence of these cardiovascular RFs and intermediate phenotypes, using random sampling of adult dwellers living in 2 adjacent cities. Strict definition of phenotypes was planned: subjects were observed twice, and several hemodynamic and other biological variables measured at least 3 months apart.

Results: Three thousand thirty-eight subjects were enrolled, and extensive data collection (including central and peripheral blood pressure, pulse wave velocity), sample processing, and biobank edification were carried out. One thousand forty-seven cognitive evaluations were performed.

Conclusions: Seeking for CV risk reclassification, early identification of subjects at risk, and evidence of early vascular aging and cognitive and renal function decline, using the strict daily clinical practice criteria, will lead to better resource allocation in preventive measures at a population level.

Key Words: blood pressure, cardiovascular risk, chronic kidney disease, cognitive impairment, arterial stiffness, early vascular aging

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Growing scientific evidence progressively changed clinical management of cardiovascular (CV) risk patients. Currently, the CV risk profile of the subject based on a wider picture of concurrent CV risk factors (CVRFs) must be considered. Tailoring CVRF control to the CV risk profile of the individual is, therefore, the current recommended strategy to prevent and delay the establishment of CV disease (CVD) and the progression on the CV continuum, as defined by Dzau[1,2] and recently reviewed by O'Rourke et al.[3] Still, and despite growing knowledge and adjustment of clinical management of CVRFs, death by CVD is still increasing and the leading cause of mortality in the world.[4]

Effective prevention of CVRFs and CVD is dependent on the establishment of appropriate public health policies and health care resource allocation based on the correct knowledge of the local epidemiological reality. Therefore, it is of relevance to gather information related to the following questions: Is the Portuguese reality concerning CVD and cognitive decline similar to what has been registered in different European countries? If not, can knowledge gathered in populations with different CVD manifestations and risk profile open new doors in CVD research and be applicable elsewhere? Is there a correct knowledge concerning the prevalence of the different CVRFs and inherent risk profile? Are there different contributors to the establishment of CVD and dementia? Can new concepts on risk of CVD development be applied to recognize subjects at risk?

To answer these questions, we propose to carry out an epidemiological study evaluating the CV risk profile of the population of 2 adjacent cities in the north of Portugal, not only analyzing the prevalence of traditional and nontraditional RFs, but also identifying in this population the prevalence of new intermediate markers of risk and/or new intermediate phenotypic expressions of progression to CVD or target-organ disease (heart, brain, and kidney). Ultimately, we seek to find a global CV risk and subclinical CVD picture of the population, which will guide future clinical search of individuals at risk through early reclassification of their CV and cognitive risk status.

Objectives

A cohort study was designed to evaluate a representative sample of the adult population of 2 adjacent cities in the north of Portugal: Guimarães and Vizela. Using a different methodology of approach and strict definition of criteria, the main objectives of this study are as follows:

1. to establish the prevalence of traditional (hypertension, diabetes, dyslipidemia, overweight, tobacco use, metabolic syndrome) and nontraditional (chronic kidney disease [CKD], hyperuricemia, salt consumption, abdominal obesity) CVRFs.
2. to evaluate the normal distribution of pulse wave velocity (PWV) and central blood pressure (BP) values in the

population and establish the prevalence of arterial stiffness and early vascular aging (EVA) signs.
3. to define the prevalence of established CV and renal disease and evaluate the existence and extension of target-organ damage (TOD) (arterial bed, heart, kidney, and brain) in subjects with added CV risk.
4. to establish the population's risk profile (using the European Society of Hypertension [ESH][5] risk classes and the SCORE [Systematic COronary Risk Evaluation] classification)[6,7] and identify the fraction that would be reclassified in terms of risk assessment due to the determination of EVA syndrome and/or subclinical organ damage (as evaluated by arterial stiffness and kidney function studies), allowing for a precocious clinical intervention or treatment intensification.
5. to evaluate the existence of an association between signs of macrovascular disease (arterial stiffness) with both different subtypes of metabolic syndrome and the accelerated development of cognitive deterioration.

MATERIALS AND METHODS

Study Consortium and Ethical Issues

To achieve the proposed goals, a protocol of collaboration was established between 3 different institutions: The Centro Hospitalar do Alto Ave (hospital reference center); The Agrupamento de Centros de Saúde (ACES–Group of Community Primary Health Care) Guimarães/Vizela (coordinating the activity of all the 13 primary community health care centers [PCHCCs] that operate in the area); and the Life and Health Sciences Research Institute, Minho University. The project was submitted to and approved not only by the ethics committee of the Administração Regional de Saúde do Norte (Health Administration for the North Region) but also by the National Commission for Data Protection.

Study Type, Sample Selection, and Subject Recruitment

We designed a cohort study (prepared for a longitudinal evaluation) evaluating a representative sample of the population of the 2 previously mentioned cities. We did not intend to obtain data that would be extrapolated to the national population as some characteristics of the population of these 2 cities (age and socioeconomic distribution) are different from the rest of the country (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JIM/A21).

There is no direct clinical intervention by the investigators, and no invasive procedure beyond blood sample collection in a peripheral venous access was programmed.

Participants have been randomly appointed through a random sampling method performed based on the list of citizens currently living in Guimarães and Vizela. In Portugal, every citizen must be registered in the PCHCC of his/her residence area. We first compared the information concerning the characteristics of citizens living in Guimarães/Vizela (INE, 2006) and the same information of those with an actual registry in one of the primary care facilities operating in the 2 cities, finding that the difference between both lists was inferior to 2%, therefore allowing us to state that, for practical use, the populations enrolled in PCHCC and living in Guimarães/Vizela are virtually the same. Portugal, like several European countries, does not collect information on ethnicity of the resident population; the overwhelming majority of its population is white. Ethnicity was not therefore considered as a factor in the study. Foreign residents in these 2 cities represent 3.6% of the population, and most of them are of European origin (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/JIM/A21).

Bearing in mind the available information regarding the characteristics of the population of Guimarães and Vizela and the characteristics that we intend to study, a representative sample of that adult population (≥18 years of age) stratified by age was defined previewing the necessity of including 4000 individuals (95% confidence interval with an estimation error inferior to 2%, considering a 25% safety margin to cope with nonadherence and dropout rate between visits). At the same time, and anticipating a higher nonadherence and dropout rates on younger and professionally active individuals, the number of randomized individuals to enroll was divided unevenly according to their age (2000 individuals would be <35 years of age, 1000 subjects would have 35 and 65 years of age, and 1000 subjects would be >65 years). Individuals registered in the local PCHCC and corresponding to the stratification characteristics were randomized as previously mentioned. Family doctors in charge of the randomized individuals have then been contacted, explained the goals of the project, and equipped with information material—they were afterward responsible to contact the subjects and obtain their written consent form to participate. It was therefore clear that only randomly assigned subjects could be enrolled and that no volunteers or physician-selected subjects would be included. If the subject refused, the general practitioner could not replace him/her with a volunteer or with someone from his/her practice. Only randomized subjects were accepted. Pregnant women and subjects unable to move or bedridden were excluded.

Criteria Definition

In accordance with the strict methodology already described, the following criteria to define conditions were chosen:
1. blood pressure categorization and hypertension definition according to the ESH 2007 guidelines[5] or whenever a subject was taking antihypertensive medication; 3 measurements under recommended conditions were taken using a validated device (Omron 705-IT; OMRON Healthcare Europe B.V., Hoofddorp, The Netherlands), and the mean of the last 2 measurements was used;
2. diabetes mellitus and glucose metabolism conditions according to the American Diabetes Association,[8] or whenever a subject was taking antidiabetic medication;
3. dyslipidemia, metabolic syndrome, abdominal obesity, and family history of premature CVD according to ESH 2007 definition[5] of CVRFs;
4. glomerular filtration rate categorization, microalbuminuria, proteinuria, and CKD definitions according to the National Kidney Foundation[9];
5. overweight and obesity according to criteria established by the fifth European Joint Task Force on Cardiovascular Disease Prevention[10];
6. salt consumption will be estimated using the renal excretion of sodium measured in a valid 24-hour urine collection;
7. pulse wave velocity and central BP will be measured using the Sphygmocor device (AtCor Medical Pty Ltd, New South Wales, Australia) and calibrated using the individual's sitting brachial BP;
8. the definition of hypertension, diabetes, CKD, microalbuminuria, or proteinuria will respect the existence of 2 agreeing measurements taken at least 3 months apart; and
9. cognitive function evaluation and cutoff definitions were done using different tools, as detailed elsewhere,[11] and allowing for the analysis of global, executive, and memory functions.

Research Team

A team of 88 researchers (medical doctors, cardiopneumology technicians, psychologists, and nurses) was assembled to observe the subjects and collect the data. A software tool was built to function as an electronic case record form, containing prevalidated and standardized questions and/or compulsory recording items to all the subjects observed. All the researchers involved were engaged in training sessions before beginning subject's observation, and standardization of procedures, measurements, and recording were ensured. A calendar of activities was designed to be followed for 2 years (86 observation dates).

Subject's Observations

Every subject was considered as enrolled after his/her family doctor had contacted him/her and was explained the study goals and procedures, and provided a signed written consent form. Subjects are to be observed twice at their PCHCC, on Saturday mornings (the 2 observations are programmed to occur at least 3 months apart).

Whenever the team of researchers was scheduled to visit a particular PCHCC, the enrolled subjects were contacted by telephone during the preceding week, remembering the time schedule and instructing them to bring their prescribed medication, to observe fasting for at least 8 hours (including alcohol and caffeine/caffeinated beverages), and to refrain from smoking until clinical evaluation, BP measurement, and blood/urine samples collection were finished. All the data/all subject observations were collected/performed in the morning, following the same protocol during the entire study period.

At their first visit, subjects were submitted to a clinical interview collecting information regarding relevant socioeconomic, clinical, and family information; clinical parameters measurement—weight, height, abdominal perimeter, and BP (3 measurements in optimal conditions); PWV and central BP measurements (using Sphygmocor device); electrocardiogram; and biologic specimen collection—blood and occasional urine samples (Fig. 1).

At their second visit, subjects were asked to repeat the clinical parameters measurement (above described), collect biological specimen: blood and occasional and 24-hour urine samples, and perform a neurocognitive evaluation (in individuals >50 years of age). Prescription drugs were once more recorded for every participant (Fig. 2).

Follow-up information will be gathered through contact with the subjects themselves and through their family doctors, as scheduled and previewed in the written consent form. Subjects older than 50 years, and after providing written consent, will be invited to perform a brain magnetic resonance imaging study, as a supplementary evaluation.

Central Laboratory Workup

All the collected blood and urine samples (occasional and 24-hour collections) will be processed in 1 central laboratory (the Clinical Pathology Department of the Centro Hospitalar do Alto Ave), ensuring standardized measurement techniques and result outputs. On the week preceding each evaluation, a kit containing prelabeled collection tubes was produced for every subject to be evaluated on the upcoming Saturday. Upon arrival, blood and urine samples were processed, and plasma, serum, and urine samples of each participant (in each visit) were frozen and subsequently stored at −82°C, allowing for the progressive edification of a sample bank.

Statistical Analysis

All the collected information will be included in a database that will be subjected to a predefined statistical analysis to provide answers to the initial queries. The database was constructed in due respect of the national and international guidelines to ensure the protection of the clinical data. This cross-sectional study will be based on a representative sample collected by stratified random sampling from the database comprising all the subjects listed in all the health centers of the 2 cities, comprising a total of 183,146 citizens. Prevalence of different studied characteristics will be estimated and calculated by demographic characteristics (age group, sex, education level) and RFs. The resulting database will be a very large one, comprising more than 2 million cells. Statistical data analysis will explore the associations between variables, using regression models so that predictive models can be built for the relevant variables. Moreover, similarities between subjects will be studied so that the possible existence of clusters can be identified. Also, other multivariate analysis, such as principal component analysis will be studied.

RESULTS

Of the 4000 subjects randomly selected, 3038 accepted to participate in the study. During the last 2 years, they have been observed according to the established and already described plan. A team of 88 researchers from 17 different clinical institutions performed more than 5580 patient observations, blood and urine sample collections, and predetermined examinations (electrocardiogram, PWV, central BP), including 1047 cognitive evaluations (in subjects >50 years of age). A biobank, containing more than 10,000 samples of plasma, 10,000 samples of serum, and 5000 samples of urine, is appropriately accommodated in our University. In Supplemental Table 3 (Supplemental Digital Content 1, http://links.lww.com/JIM/A21), the number of subjects observed, distributed by gender and age strata are presented for visits 1 and 2.

DISCUSSION

CVRFs and CVD in Portugal

Portugal is the only Western European state in the top 10 countries of the world where stroke exceeds ischemic heart disease's (IHD's) standardized mortality rate.[12] The incidence of transient ischemic attacks and stroke is known to be very high in Portugal and particularly in the northern region (up to 3 strokes and 0.67 TIAs per year/1000 inhabitants[13,14]). Ischemic heart disease has a complete different pattern of incidence in Portugal; the country bears the second lowest standard mortality rate by IHD in Europe[15] and a particular geographic pattern of distribution of its incidence,[16] with the northern coastal area recording the lowest admission and mortality rates—data that enhance the contrast with stroke incidence. With the strict CVR phenotyping methodology here presented, we aspire to uncover unclear contributions to this paradoxical CVD manifestation.

The prevalence of different CVRFs and the incidence of CV events (CVEs) in the Portuguese population have received greater attention in the last decade. Studies with different measurement and population sampling methodologies have found a national prevalence of hypertension ranging from 41.2% to 42.6%,[17–19] with the diagnosis of isolated systolic hypertension estimated to affect 34.7% of Portuguese individuals older than 55 years[20] and prehypertension afflicting 39.5% of the adult population.[17] However, the use of BP values measured in a single visit and the recruitment strategies used raised criticisms, arguing an overestimation of hypertension prevalence and/or underestimation of its awareness and treatment rates. Overestimation of hypertension and mean BP values with single visit strategies have been reported[21–23] (ranging from 12.6% to 35% for hypertension in Portugal). Surprisingly, the number of

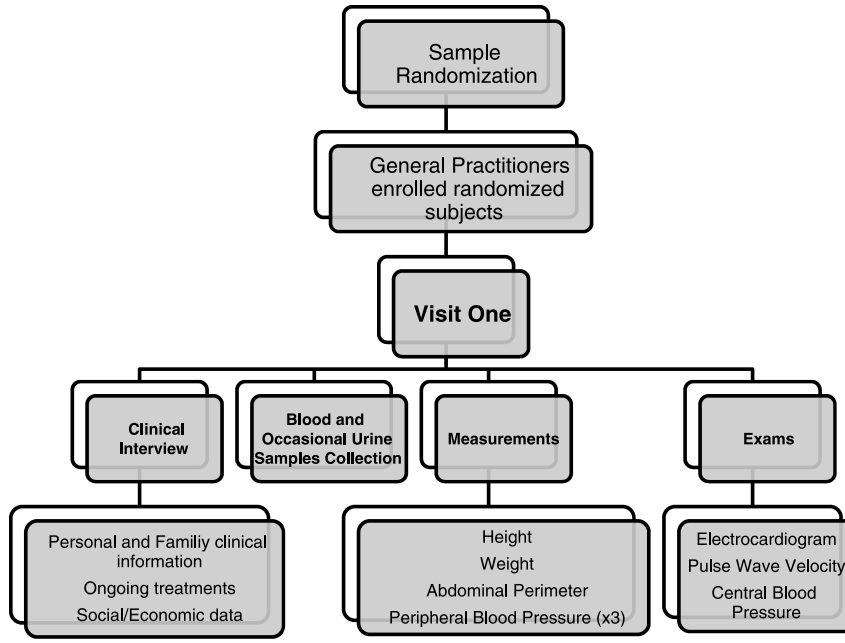

FIGURE 1. Study procedures outline (visit 1).

studies using at least a 2-visit strategy is very scarce worldwide.[24,25] The prevalence, awareness, treatment, and control rates of hypertension in Portugal are not different from those in other southern and western European countries.[25] The paradox lies on the concept that the Portuguese hypertension prevalence as well as BP mean values have been trending down in the last decades,[26] at a rate that is reported to be superior to that observed in other Western European countries,[27] and still the incidence of CVE and particularly stroke has kept disproportionally elevated, even if presenting a tendency to decline.[28,29] We aim to produce more precise estimation of BP levels and hypertension prevalence as well as the quantification of overestimation of BP and hypertension that results from single BP evaluation (with the consequent underestimation of BP treatment and control).

Other CVRFs have been less studied in Portugal. The worldwide trend in mean fasting plasma glucose (FPG) has slowly increased, and the age-standardized prevalence of diabetes ranges from 9.8% in men to 9.2% in women.[30] Portuguese estimations of the prevalence of diabetes (single visit strategy) range from 11.7% to 13% of the adult population,[31,32] evidencing a higher prevalence of the disease than globally recorded, especially concerning men; the prevalence of prediabetes was estimated in 23.3%.[31] According to the International Diabetes Federation, the prevalence of diabetes in Portugal was the highest recorded in the European countries analyzed.[33] We could not find any national trend analysis of diabetes and FPG levels. The relevance of mean FPG levels increases with evidence linking growing levels with CVD, independently of the existence of diabetes.

Chronic kidney disease and microalbuminuria are well recognized CVR factors.[34–37] An estimation of CKD (based on a single measurement of serum creatinine levels and on information from a national registry of patients under renal replacement therapy) reported a 6.1% prevalence in the Portuguese adult inhabitants,[38] similar to reports in other European countries.[39] However, more

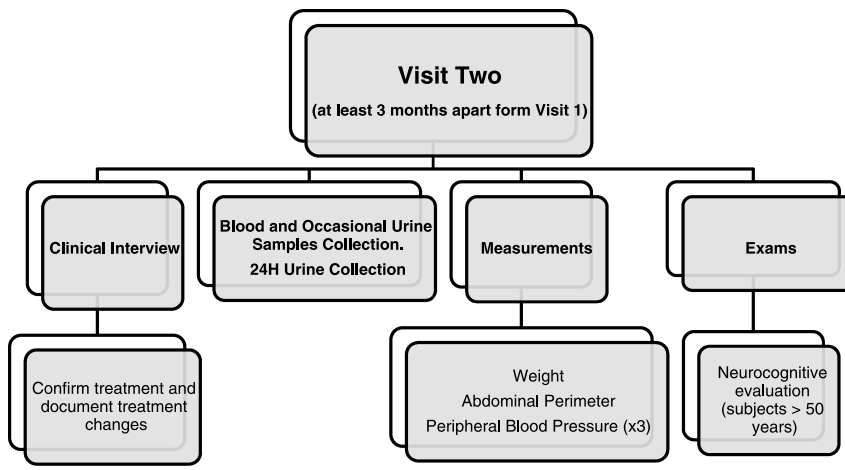

FIGURE 2. Study procedures outline (visit 2).

accurate methods of staging CKD have been established, combining glomerular filtration rate estimates and albuminuria[40,41] and exhibiting a better association both to the risk of progression to end-stage renal disease and to the CVR in the population, throughout all age classes.[10,42,43] Therefore, a more accurate definition of CKD prevalence in Portugal, using both markers, is missing. Only for Portuguese hypertensive subjects[44] can a report of prevalence of microalbuminuria (24%) be found.

Regarding dyslipidemia, a systematic review of the literature found several difficulties in aggregating results from different studies in Portugal, with different population groups, measurement methodologies, selection bias, and cutoff values.[45–47] Main extractable results revealed mean serum total cholesterol values greater than 200 mg/dL, 20% of the population recording cholesterol levels greater than 240 mg/dL, and low high-density lipoprotein and high triglyceride levels affecting 25% and 30.7% of the population, respectively.[48] In Portuguese subjects treated with statins, 68% and 62.9% did not have their total cholesterol and low-density lipoprotein cholesterol levels controlled, respectively.[49] Worldwide, a slow and small global trend of decreasing levels of total cholesterol has been recorded in the last 3 decades, estimating current mean levels in Western Europe as 212.7 mg/dL.[50]

Metabolic syndrome has been estimated to afflict 27.5% of the national population and 23.9% of a regional urban sample of adult dwellers[48,51]; male sex was predominantly presenting the syndrome from 18 to 49 years, with females being more afflicted in older age groups.[48] Overweight and obesity prevalence are also growing in the Portuguese population, with a composite prevalence of 66.6% and 57.9% for men and women, respectively.[52,53]

In summary, we believe that it is important to look simultaneously at strictly determined BP and FPG mean values, lipid serum levels, estimated glomerular filtration rate, and albuminuria when trying to understand the different CVE rates registered in Portugal (more stroke than IHD), and to look for other explanations of these same CVE that go beyond individual prevalence of hypertension, diabetes, and CKD (cumulative RFs, intermediate CV phenotypes, CV risk reclassification strategies—global CVR stratification).

Recent Concepts of Cardiovascular Risk and CVD

New methods of evaluating CVD and CVR have been proposed. Measurement of arterial stiffness (through PWV) has been accepted as portraying the reflex of different CVRFs in the arterial structure, becoming itself a marker of CVR with independent predictive power of CVE beyond and above traditional CVRFs, allowing for risk restratification of significant proportions of the population; the predictive ability of arterial stiffness is higher in high-risk groups, but it retains its discriminative power both in the general population and hypertensive subjects independently of age.[54–56] Recent European guidelines establish PWV values greater than 10 m/s as TOD,[57] and reference values for the European population have been published.[58]

In Portugal, arterial stiffness has been raising growing interest. In a pioneer study, a concurrent determination of salt intake and PWV in a convenience sample of 426 subjects could record a high salt intake and its independent correlation with PWV values (r = 0.256, after adjustment for age and BP).[59] Another project has determined PWV values to subjects referred by their clinicians to 3 clinical centers[60]; a predictive value of PWV for CVE could be defined for values of PWV greater than the 95th percentile. Interestingly, the unadjusted risk ratio for stroke was 6.68, and that for myocardial infarction was 5.4. In a subsample of 668 young subjects (mean age, 40 years) with low CV risk and significant male predominance (60%), the authors statistically extrapolated "normal" PWV values for 16 different age classes (8 per sex).[61]

Central blood pressure and central hemodynamic indexes are another aspect of vascular evaluation that can be determined safely and noninvasively. Its association with the development of TOD and CVD has been well documented.[62] A recent meta-analysis has established their values as independent predictors of CVE and all-cause mortality,[63] and interest has been increasing as CBP is thought to better reflect the pressure load sustained by vascular circulation of the brain, kidney, and coronary arteries.[64–67]

Early vascular aging is a functional and clinical concept[68] in fast development: the normal age-dependent process of vascular change in structure and function can, in susceptible subjects or under the influence of different factors (including CVRFs), be accelerated and/or be replaced by a pathologic process of vascular remodeling, leading to premature atherosclerosis and CVD.[69–73] The definition of EVA is dependent on arterial stiffness measurements, but debate is ongoing to better refine the criteria to use. The question remains if by identifying subjects with early vascular changes, one could reclassify low CV risk subjects in higher CV risk classes and treat early and more intensively to prevent CVD.[72,74] No evaluation of EVA, PWV, or CBP has ever been attempted in the Portuguese population. The CVR reclassification value of these variables in the Portuguese CVD setting is something we aim to establish with the current study.

Vascular Aging and Brain Aging

Subclinical organ damage is one important parameter to classify subjects concerning their total CVR. The brain is particularly challenging (when it comes down to evaluate TOD induced by CVRFs or CVD) as there is no simple way to identify subjects with subclinical manifestations, and TOD is defined only when a documented cerebrovascular event has been registered. Much has been debated concerning the influence and contribution of vascular disease, CVRFs, or hemodynamic variables to the acceleration of the brain aging process and/or the establishment of cognitive decline, and the concept of vascular cognitive impairment is well established.[75,76]

With an aging population, progression to dementia and the increase in the number of dependent subjects are clearly a concern; estimation of the prevalence of mild cognitive impairment ranges from 10% to 20% in adults older than 65 years,[77] which obviates the need to early identification of subjects at risk of cognitive decline and control of factors that contribute to dementia. The LADIS (Leukoaraiosis and Disability) study[78–80] has shown that older independent subjects with white matter hyperintensities progress to disability and functional decline with the more severe changes relating to higher risk of decline.[78] An association of lacunar infarcts with cognitive decline and white matter hyperintensities has also been considered (hinting for a spectrum of different expression of small vessel disease),[79] and an independent effect of CVRFs in cognitive decline has also been reported.[80] In Portugal, the prevalence of cognitive impairment has been studied in a regional sample of the population, and a report of 12.0% to 16.8% (urban-rural areas, respectively) has been described.[81]

Evidence fueling the merit of a precocious and preventive identification of subjects at risk of progression to dementia or cerebrovascular disease comes from the Framingham study, where changes in white matter microstructure and reduction in gray matter volume could be seen in association with growing levels of BP in young subjects.[82] With the knowledge that

arterial stiffness measurements can be associated and predict cognitive decline[83–85] and silent cerebral small vessel disease,[86] one could aspire to an early recognition of subjects at risk using PWV measurement.

CONCLUSIONS

Here we reviewed the literature reporting the state of knowledge concerning CVD, CVRF prevalence, and cognitive decline estimates of the Portuguese population, comparing it with what is known abroad. Based on this evidence, we developed the rationale of the Guimarães/Vizela Study, a multimodal population-based cohort study to determine global CV risk and disease, a comprehensive approach to determination of global CV risk and risk reclassification perspectives, with the ultimate goal of early detection of subjects at risk for CVD, renal disease, cognitive impairment, and dementia.

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