The *ZARADEMP Project* on the incidence, prevalence and risk factors of dementia (and depression) in the elderly community: I. The context and the objectives

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ABSTRACT – *Background and Objectives:* The public health dimension of the problem of dementia and depression in the elderly population is well documented, but epidemiological data are generally considered to be insufficient and, at times, contradictory. This paper identifies relevant research areas for the *ZARADEMP Project*, which follows the Zaragoza Study (or *ZARADEMP 0)* and is part of both *EURODEM* and *EURODEP Studies.*

Methods: Review of the literature. Hypotheses emerging in previous studies of this research group.

Results: The following relevant objectives to study in relation to dementia (and depression) have been identified: a) potential variations over time in the prevalence rate; b) provision of reliable estimations of incidence rates, specific for age and gender; c) data about the course and natural history of so called "mild cognitive deficit"; d) association between hypothesized risk factors and cases of dementia (and depression) and its most frequent

subtypes; and e) testing of hypotheses related to the overlap between dementia and depression and, specifically, to what extent depression has an increased risk for DAT. Other objectives of the study are also reviewed, in particular the cross-cultural comparison of findings in Zaragoza and in other European cities incorporated in both *EURODEM* and *EURODEP* Studies. The importance of maintaining good, contemporary methodological standards is emphasized.

Conclusions: A number of relevant research areas in the epidemiology of both dementia and depression in the elderly have been identified. Case-control studies based on incident cases of dementia of the Alzheimer's type (DAT) to adequately assess risk factors seem particularly timely.

Introduction: prevalence and incidence of dementia

Classical epidemiological studies have suggested that dementia and depression in the elderly pose a major public health problem (Copeland *et al.* 1987, Mellow 2003). However, a high proportion of mental disorder cases in the community remain untreated (Cole *et al.* 1999). This was also suggested by the *Zaragoza Study*, which was the first psychiatric report about the prevalence of dementia and depression in a Spanish speaking country, but also in Southern Europe, which investigated a representative community sample of the elderly with standardized methods of assessment specifically developed for this age group, as well as standardized diagnostic criteria and case levels of illness (Lobo *et al.* 1995).

While prevalence studies of dementia are abundant, the stability of rates of dementia in the same geographical area has rarely been addressed (Rocca *et al.* 1998). The *ZARADEMP Project* follows the *Zaragoza Study*, which we now call *ZARADEMP "0"*. Its first objective was to test hypotheses related to potential variations over time in the prevalence rate of dementia that might

eventually be traced to environmental circumstances. It was also designed to provide reliable estimations of incidence rates of dementia, specific for age and gender (Lobo *et al.* 1992). We observed in the follow-up of *ZARADEMP "0"* the exponential increase of the incidence rate with the increase in age reported by most authors (Lobo *et al.* 1997, Rocca *et al.* 1998, Di Carlo *et al.* 2002, Jorm and Jolley 1998). However, we also reported a slowing down of the acceleration of rates in the very old. This slowing down needs clarification (Gao *et al.* 1998), since the low numbers in the numerator in several studies including ours could account for the low rate in this age group (McGee and Brayne 2001). A third objective of the Project was to document the course and natural history of so called "mild cognitive deficit". This is a subject of recent interest in view of the reported high conversion rate into dementia (Petersen *et al.* 2001).

Risk factors of dementia: the main objective

The principal objective of the *ZARADEMP Project* was to document the association

between hypothesized risk factors and cases of dementia and its most frequent subtypes, dementia of the Alzheimer's type (DAT) and vascular dementia (VD), so that preventive measures might eventually be instituted (Lobo *et al.* 1992). In relation to DAT, only an increasing age, the presence of the apolipoprotein-epsilon4 allele, particularly for late-onset DAT, familial aggregation in cases and Down's syndrome are considered to be firmly established risk factors (McDowell 2001). The finding about the steep increase in the prevalence of Alzheimer's type disease with age is the most consistent one in the international literature (Hofman *et al.* 1991, Jorm *et al.* 1987*)*. Therefore, attention might be drawn to the null hypothesis and its implications, namely, that cognitive disturbances identified in the elderly might be viewed as a manifestation of senescence in which specific extrinsic influences are unnecessary to account for the pathology observed. However, this notion has to be immediately qualified. Even if age is the most important risk factor for DAT, it may conceal the effect of other weaker risk factors in population studies. Wide variation of genetic and environmental factors that can influence primary degenerative dementia have been identified (Van Duijn and Hofman 1991).

Most reports have suggested the association between DAT and female gender (Andersen *et al.* 1999, Copeland *et al.* 1999a). However, new studies are required, since some reports are discrepant (Lobo *et al.* 1995, Sandberg *et al.* 2001). Similarly, in support of the "cognitive reserve hypothesis" (Qiu *et al.* 2001), most studies, including ours (Lobo *et al.* 1995), have also reported a striking association between DAT and low education (Letenneur *et al.* 1999). However, it remains to be determined to what extent other factors may influence the risk. For example, age has been reported to modify the

risk atributed to female sex (Ott *et al.* 1998, Ruitenberg *et al.* 2001); and sex (Ott *et al.* 1999) or social factors (Meguro *et al.* 2001) have been reported to modify the risk attributed to low education.

In view of insufficient or contradictory findings, new research should also be performed to clarify at a population level the role that other factors may play in the cause of DAT (Slooter *et al.* 1998, Lindsay *et al.* 2002). Such factors may be biological, such as head injury, alcohol or tobacco consumption, Parkinson's disease, estrogen deficiency in women or abuse of some legal drugs, including anaesthesia before the age of 50 years; or factors recently considered, such as medical comorbidity (Doraiswamy *et al.* 2002) or exposition to potentially toxic products, in particular products that may be plausible biological factors (Tyas *et al.* 2001). Potential risk factors to investigate may also be psychosocial, and include social problems, living in rural areas, problems in early-life and adolescent environment, life style or social environment, or the impact of nursing home placement (Moceri *et al.* 2000, Smith *et al.* 2000, Lee *et al.* 2002). The protective effect of non-steroid anti-inflamatory drugs (NSAIDS), wine consumption or coffee consumption or regular physical activity also needs clarification (Lindsay *et al.* 2002). Finally, the contribution to DAT of the classical risk factors for vascular diseases is one of the most promising findings, (Stewart *et al.* 1999, Meyer *et al.* 2000a), particularly in relation to late-onset DAT (Kalman *et al.* 1999), but these studies require replication. Similarly, the potential protective role of antihypertensive medication in DAT is most promising (in't Veld *et al.* 2001), but confirmatory studies are required.

There is also abundant research evidence to support new studies to document the

association between hypothesized risk factors and vascular dementia (VD). While the importance of risk factors such as hypertension, diabetes, apolipoprotein-epsilon 4, transient ischaemic attacks (TIA), hyperlipidemia or smoking tends to be confirmed in recent reports (Meyer *et al.* 2000a, Meyer *et al.* 2000b), new studies are needed to confirm the suggested modulating effects of factors such as gender (Hebert *et al.* 2000). Most studies have reported that VD is more frequent in men (Di Carlo *et al.* 2002, Copeland *et al.* 1999a, Ruitenberg *et al.* 2001), but some are discrepant (Hebert *et al.* 2000). New studies should also try to confirm the potential risk for VD of other factors suggested by recent research, such as living in a rural area or in institutions, depression, occupational exposure to fertilizers or fumigants (Hebert *et al.* 2000); or the protective effect of factors such as taking antihypertensive agents (Guo *et al.* 2001, in't Veld *et al.* 2001) or regular exercise for women (Hebert *et al.* 2000).

Methodological standards in psychiatric epidemiology in the elderly

The experience with epidemiological studies of dementia suggests the importance of maintaining good methodological standards (Launer *et al.* 1992a, Riedel-Heller *et al.* 2001). It is now clear that both, prevalence and incidence studies of dementia should investigate representative community samples which include institutionalized and non-institutionalized elderly. Standardized structured methods of screening and case ascertaintment instruments specifically developed for the elderly should be used (Andersen *et al.* 1999), and the cut-off

points individualized and previously tested in the specific culture (Lobo *et al.* 1995). Similarly, standardized diagnostic criteria and case levels of illness are now commonly required (Black *et al.* 1990, Riedel-Heller *et al.* 2001).

In studying risk factors, case-control studies may be powerful, and are classical in this field (van Duijn and Hofman 1991). However, conclusions of studies based on hospital cases or on population, prevalent cases should previously discuss potential selection or information bias. At the time the *ZARADEMP Project* and other studies of the *EURODEM Workgroup* were designed, it was generally agreed that there is a need for case-control studies based on incident cases of dementia to adequately assess risk factors (Launer *et al.* 1992b, Lobo *et al.* 1992). Furthermore, special techniques may be required in data analysis. Latent variable analysis suggests that some potential risk factors of dementia are positively correlated with each other and could be conceptualised as correlated, observable manifestations of more unitary underlying constructs (Liu *et al.* 2001).

New inquiries into the epidemiology of depression in the elderly

There are also reasons to support the inclusion of new studies of depression in a community investigation of dementia, and some of them will be reviewed here. While prevalence studies are abundant, new studies are needed to document the age and sex specific incidence of depression (Green *et al.* 1992, Jorm 1995). In relation to risk factors, the association between depression and factors such as social problems has been

consistently found in different studies (Kopp *et al.* 2000, Ostler *et al.* 2001). Similarly to most reports, depressive conditions in *ZARADEMP 0* were higher in women when compared to men (Weissman and Klerman 1985), and also in lower educational levels (Weissman *et al.* 1991, Lobo *et al.* 1995). Furthermore, we reported during the same investigation wide differences of prevalence of both, depression and depressive symptoms between our city and other European cities (Copeland *et al.* 1999b, Copeland *et al.* 1999c), and the influence of social and environmental factors was suggested. By itself, however, this association does not reveal a causal connection, since social problems have also been reported as a consequence of depression (Van Hook 2003). Other suggested risk factors for depression include life insatisfaction, loneliness, recent life events (Green *et al.* 1992) or disability (Cole and Dendukuri 2003), or new factors such as smoking (Jorm 1999). Further inquiry is essential before firm conclusions may be drawn in relation to both, social causes and social consequences of depression, since support from prospective studies and from case-control studies is limited (Conwell *et al.* 2002). The issue may be clarified in a community study such as the *ZARADEMP Project*.

An overlap between dementia and depression was also reported in *ZARADEMP 0*, but a complex, multi-facetted relationships between both conditions has been described by different authors (Mahendra 1985, Rao 2000, Harwood *et al.* 2000). We challenged the notion put forward by some authors (Hendricksen *et al.* 2004) about the possibility that in the elderly they might be common conditions due to dysfunction in an aging brain, since contrary to dementia, the prevalence rate of depression did not increase systematically with age (Lobo *et al.* 1995). Furthermore, our data did not support an age effect on the comorbidity found, but authors such as Ames (1990) have questioned the validity of the distinction in the very old in view of the overlap and the poor outcome of patients diagnosed as depressed (Sharma *et al.* 1998, Saz *et al.* 1999). Specifically, one of the objectives in the *ZARADEMP Project* was to document to what extent depression has an increased risk for DAT (Jorm 2000, Weiner *et al.* 2002), rather than being a prodromal or early manifestation of dementia or an emotional, adjustment reaction to the awareness of the illness (Wetherell *et al.* 1999, McDowell 2001). Among all disciplines involved in the epidemiological study of dementia, psychiatry is in a unique position to investigate this subject.

Other objectives of the project: cross-cultural comparisons

Other objectives of the study were to document: a) the course and natural history of both dementia and depression in this population, aiming at the identification of subtypes which might suggest different aetiopathogenetic mechanisms or different intervention strategies (Jagger *et al.* 2000, Dartigues 1999); b) the prevalence, incidence and associations of disability; c) the prevalence, incidence and implications of physical morbidity, as well as non-cognitive, non-depressive morbidity; and d) the mortality outcomes and factors influencing them, in an attempt to replicate in larger samples, and controlling for methodological problems, the findings in previous studies (Sharma *et al.* 1998), including ours (Saz *et al.* 1999). The database could also be used in the future to test in this cohort of

the elderly new hypotheses related to advances in the field of dementia and depression.

Finally, the *ZARADEMP Project* was designed to compare incidence rates of dementia, as well as depression, and risk factors for both conditions found in Zaragoza with data reported using the same methods in other European cities during the *EURODEM* (Launer *et al.* 1992b) and *EURODEP* (Copeland *et al.* 1999b) studies respectively. Differences found in prevalence rates of both dementia (Lobo *et al.* 2000) and depression (Copeland *et al.* 1999c) in these previous reports, which include preliminary data from Zaragoza, are encouraging, since substantial epidemiological reasoning would be prompted if cross-national differences are confirmed. However, prevalence studies may be influenced by duration and fatality rates. Therefore, comparative studies of incidence rates have more epidemiological interest. In relation to this, geographical differences have also been suggested in indicence reports of dementia (Jorm and Jolley 1998, Waite *et al.* 2001, Chandra *et al.* 2001), even when a common design was used in the participating centers (Fratiglioni *et al.* 2000). Preliminary data from Zaragoza were also included in this last study, and now require confirmation.

Specific hypotheses for each objective have been formulated, and will be presented and discussed in the coming papers.

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