Late life depression and incident activity limitations: influence of gender and symptom severity.

Isabelle Carrière[a,b,*] PhD, Laure Anne Gutierrez[a,b] MSc, Karine Pérès[c,d] PhD, Claudine Berr[a,b] PhD, Pascale Barberger-Gateau[c,d] PhD, Karen Ritchie[a,b,e] PhD, Marie Laure Ancelin[a,b] PhD

[a] Inserm, U1061, Montpellier, F-34093, France

[b] University Montpellier1, Montpellier, F-34000, France

[c] Inserm, U897, Bordeaux, F-33076, France

[d] University Victor Segalen Bordeaux 2, Bordeaux, F-33076, France

[e] Faculty of Medicine, Imperial, College, St Mary's Hospital, London, UK

[*]Corresponding Author

Isabelle Carrière

Inserm U1061

Hopital La Colombière,

BP 34493

34093 Montpellier Cedex 5, France

Tel: +33 499 614 691

Fax: +33 499 614 579

Email: isabelle.carriere@inserm.fr

Word count: 4027

Abstract

Background

Mental disorders, especially depression, are one of the principal causes of disablement**.** Previous research has been limited partly due to the failure to take into account sub-syndromal states and the very large number of candidate mediating and confounding factors.

Methods

Longitudinal associations between baseline depressive symptomatology and activity limitations were examined in a community-dwelling elderly cohort of 3191 participants. Mixed logistic models were used to determine associations between mild or severe depressive symptoms (Center for Epidemiologic Studies-Depression Scale, CES-D), and 7-year incident disability on four limitation scales assessing instrumental and basic activities of daily living, mobility using the Rosow and Breslau scale, and social restriction.

Results

In men, mild depressive symptomatology was associated with increased incident limitations on instrumental activities of daily living (IADL) (odds ratio (OR) (95%CI)=5.07(2.25-11.42)). In women, severe depressive symptomatology was related to social restriction (OR(95%CI)=2.36(1.31-4.25)), IADL (OR(95%CI)=1.89(1.13-3.15)) and activities of daily living (OR(95%CI)=11.15(3.43-36.23)). Men and women with a 2-year increase in CES-D score were highly at risk for social restriction and limitations in mobility and IADL.

Conclusion

Depression is an independent predictor of disability in the elderly population; the relation is gender-dependent and varies with symptom load.

Key words: Aged; Longitudinal studies; Disability evaluation; Depression; Gender differences

Introduction

Mental disorders are one of the principal causes of disablement; the Global Burden of Disease reporting that neuropsychiatric conditions account for up to a quarter of all Disability-Adjusted Life-Years (DALYs) (Murray and Lopez, 1996; Prince et al., 2007). Depression in particular is associated with high mortality and disability, accounting for 4.46% of DALYs and 12.1% Years of Life with Disability (YLDs) (Ustun et al., 2004). It is above all late life depression which significantly reduces disability-free life expectancy (Peres et al., 2008). Estimates of the life-time prevalence of major depression in elderly cohorts vary widely (3 to 19%) (Lyness et al., 1999; Ritchie et al., 2004), this variability being largely attributable to assessment methods (clinical/standardised examination/self-evaluation) and the type of depression investigated (major, minor or depressive symptoms). Most elderly people who have clinically significant depressive symptoms do not meet the full diagnostic criteria for major depression (Blazer, 2003; Rollman and Reynolds, 1999), however, sub-syndromal depression has both a high prevalence in later life and poor response to anti-depressant treatment (Kirsch et al., 2008). It may thus constitute a major cause of disability for which treatment methods are presently unsatisfactory.

A better understanding of the association between both major and sub-syndromal depression and disability constitutes an important first step in identifying alternative intervention points for therapeutic intervention. Previous research has been limited not only due to failure to take into account sub-syndromal states and the very large number of candidate mediating and confounding factors, but also the inadequacy of the disability measures used. Previous longitudinal studies have principally used partial dependency measures incorporating different items from activities of daily living (ADL) or instrumental activities of daily living (IADL) scales (Carriere et al., 2009; Schillerstrom et al., 2008). Furthermore, although gender differences have been consistently observed in the aetiology and clinical presentation of

depression, differential susceptibility to depression-related disability has surprisingly seldom been investigated. We recently reported that the association between depression and 4-year mortality is dependent both on gender and disease severity, the greatest risk being observed for men with severe depression (Ryan et al., 2008).

The purpose of this study is to examine the long-term association between depressive symptoms and incident activity limitations in a large elderly prospective community cohort, for which information on a large number of potential confounding factors was available. The analyses are based on four independent scales of activity limitation corresponding to different levels of activity and social restriction.

METHOD

Study sample

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001 (The 3C Study Group, 2003). The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. A standardized evaluation with a face to face interview and a number of clinical examinations was undertaken in the three study centres at baseline, 2 and 4 years. In the centres of Bordeaux and Montpellier this follow-up was extended with an examination at 7 years. Of the 4215 dementia-free participants included in these two centres, 408 were missing all follow-up evaluations for activity limitations (of whom 170 died) and 616 had missing data for at least one baseline adjustment variable. The present analyses were thus conducted on 3191 subjects (1617 from Bordeaux and 1574 from Montpellier; 1311 men and 1880 women).

Compared with the analysed sample, those not included in this analysis were more likely to be older ($p < 0.0001$), have lower education ($p<0.0001$), be more depressed ($p< 0.0001$), use antidepressants ($p=0.004$), live alone ($p=0.02$) and have disabilities ($p<0.0001$), cognitive impairment ($p<0.0001$), comorbidity ($p<0.0001$), visual impairment ($p=0.03$) and hearing impairment ($p<0.0001$).

Disability measures

Three complementary measurements of activity limitations were investigated as outcomes: mobility, complex or instrumental activities of daily living (IADLs) and basic activities of daily living (ADLs). Mobility was assessed according to the Rosow and Breslau scale (Rosow and Breslau, 1966) which evaluates ability to do heavy housework, walk half a mile, and climb stairs. The Lawton–Brody IADL scale was used to assess individual ability to use the

telephone, to manage medication and money, to use public or private transport, to shop, and for women only, to prepare meals and do housework and laundry (Lawton and Brody, 1969). For ADLs, participants were asked whether they needed help for any task on the Katz ADL scale: bathing, dressing, transferring from bed to chair, toileting, and eating (incontinence was not considered since it reflects organ impairment rather than functional limitation) (Katz et al., 1970). For each domain of disability, participants indicating inability to perform one or more activities without help were considered as having mobility, IADL, or ADL limitations. A fourth outcome was social restriction (confinement to bed, home or outings restricted to neighbourhood) which can be considered as participation restriction according to the International Classification of Functioning, Disability, and Health (ICF, 2001).

Depression

The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), a standardised psychiatric examination which has been validated in the general population, was used for the diagnosis of current and past major depressive episodes (MDE), according to DSM–IV criteria. Severity of depressive symptoms was assessed using the 20-item Center for Epidemiologic Studies–Depression scale (CES–D) (Radloff, 1977). For this analysis, participants were classified into one of three groups (Ryan et al., 2008). 'Severe depressive symptomatology' (Severe DS group) included participants with a current MDE or a CES–D score of 23 or over (allowing for the fact that some participants with severe symptoms did not reach DSM classification criteria, principally because of the duration of symptoms). 'Mild depressive symptomatology' (Mild DS group) was defined as a CES–D score between 16 and 22 and 'no DS' included participants with a CES–D score lower than 16. Deterioration in depressive symptoms between inclusion and the first follow-up examination was defined as an increase of 3 points or more in the CES-D score. Current use of antidepressants was

validated by presentation of the prescription or medication to the interviewer, and type of medication was noted according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification.

Socio-demographic and clinical variables

The standardized interview included questions on demographic characteristics, education level (classified in four groups corresponding to 5, 9, 12, and 12+ years of education), marital status, income, mode of living (alone or not), height, and weight. Information was obtained on type and quantity of alcohol consumption (number of units of alcohol per day; 0, 1-36, >36 g/day), tobacco use (classified as past, present or never users) as well as use of hormonal therapy (HT) (never, past, current use) for women. Detailed medical questionnaires included history of stroke, angina pectoris, myocardial infarction, and cardio-vascular surgery established according to standardized questions, history of cancer and fracture with hospitalisation during the last two years, asthma (attacks during the last year), chronic bronchitis, dyspnoea, hypertension (>160/95 mm Hg or treated), diabetes (fasting glycemia> 7mmol/l or treated) and thyroid disease. Blood pressure was measured during the interview using a digital electronic tensiometer OMRON M4. The number of chronic diseases was calculated including: hypertension, diabetes, cardiovascular diseases, respiratory diseases, dyspnoea, thyroid disease, and cancer.

Cognitive impairment was defined as a Mini Mental State Examination (MMSE) (Folstein et al., 1975) score lower than 24. Visual impairment was defined as having a corrected near visual acuity (Parinaud scale) of less than 4 or difficulties recognizing a familiar face at 4 meters. Hearing impairment was defined deafness or only able to hear a conversation when a single person speaks loudly.

Statistical analyses

Separate analyses were conducted for men and women. The Chi2 test was used to identify gender-related differences. For each indicator of activity limitations longitudinal associations with the levels of DS were established from subjects free of that activity limitation at baseline. Thus the sample size was 951 men and 954 women for mobility, 1245 men, and 1723 women for IADL, 1303 men and 1864 women for ADL and 1276 men and 1738 women for social restriction.

In longitudinal studies, the within-subject responses (repeated evaluations of activity limitations) are correlated. This correlation was accounted for by using a mixed logistic model (Carriere and Bouyer, 2002). Briefly, this model has four basic characteristics: (i) the individual time evolutions of activity limitations are entirely taken into account including possible reversion to normal state (ii) subjects with incomplete responses across time are included in the analysis; (iii) subjects do not have to be evaluated at the same time points; (iv) the model allows within-subjects dependency to vary from one subject to another, via the random part of the covariable linear combination. The SAS procedure NLMIXED was used to estimate the parameters (version 9.1).

We used univariate and multivariate models to determine if baseline DS was associated with odds of activity limitations or social restriction during follow up. After gender stratification, univariate odds ratios were adjusted for centre, age, time and interaction time*age (**Model 0**). Multivariate adjusted logistic regression included covariates that were associated with the follow-up responses ($p<0.15$ in univariate model). **Model 1** was adjusted for age, centre, time, time*age, alcohol, body mass index (BMI), smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment and HT (women only). **Model 2** was further adjusted for income, education level and living alone and **Model 3** for antidepressant treatment and past MDE.

A sensitivity analysis was also performed. The non-respondents at 7 years were contacted by telephone and invited to answer a short questionnaire exploring medication use, activity restrictions (ADL, IADL, mobility), cognitive performances (MMSE, verbal fluency test) and depressive symptoms (CES-D). Information obtained by telephone were pooled with the study data base in order to examine potential bias due to non random loss to follow-up.

RESULTS

Within this elderly community-dwelling sample, the baseline prevalence of Severe DS (major depressive disorder or CES-D ≥ 23) was 11.8% and that of Mild DS (CES-D 16-22) was 9.2%. Past MDE was reported by 40.3% of subjects with Severe DS and 20.5% with Mild DS and the mean age (SD) of first episode onset was 43.9 (16.1) years. Women had a significantly higher prevalence of Severe and Mild DS than men, were more often treated with antidepressants, and declared more frequently a history of MDE **(Table 1)**.

For every baseline disability scale except ADL, women reported activity limitations significantly more frequently than men (7.50% vs 2.52% for social restriction, 48.63% vs 26.45% for mobility, and 7.96% vs 4.59% for IADL). Compared to men, women were also less educated, more likely to live alone, have a lower incomes more visual and cognitive impairment but were less likely to have hearing impairment, comorbidity, to be overweight or obese, to smoke and take alcohol.

The analysis of the repeated activity limitation proportions was undertaken for each scale on the subjects without limitation on the considered scale at baseline. **Table 2** shows the rates of activity limitations over 7 years in men and women according to the level of baseline DS and the odds ratios of having incident activity limitations adjusted for age, centre, time and the interaction between time and age (model 0). Over the follow-up period, the probability of becoming disabled tended to increase for all the indicators and whatever the level of DS. All mixed logistic models showed a significant effect of age and age*time interaction indicating

that the effect of time on activity limitations was more pronounced in the oldest old. For ADL in men time and age were significant, but not the interaction.

Compared with men without DS at baseline, the risk of having IADL limitations during follow-up was highly significantly greater in men with Mild DS (OR(95%CI)=5.20 (2.37-11.38)) **(Table 2)**. This association was also significant for social restriction (OR(95%CI)=2.71 (1.01-7.26)) and mobility (OR(95%CI)=1.87(1.00-3.50)). In women whatever the outcome scale, baseline Mild DS was not found to be significantly related to the odds of activity limitations during follow-up. Baseline Severe DS was only found to be significant in men for social restriction (OR(95%CI)=3.85(1.05-14.04)) while in women it was highly significant for social restriction (OR(95%CI)=3.57(1.93-6.61)), IADL (OR(95%CI)=2.47(1.48-4.11)) and ADL (OR(95%CI)=13.29(4.50-39.31)).

When the mixed logistic models were further adjusted for possible confounding factors (model 3) all the preceding associations persisted except in men for social restriction and mobility. In men (**Table 3**), Mild DS was highly significantly associated with the adjusted odds of IADL limitations (OR(95%CI)=5.07(2.25-11.42)) while in women (**Table 4**) Severe DS was related to social restriction (OR(95%CI)=2.36(1.31-4.25)), IADL (OR(95%CI)=1.89 (1.13-3.15)) and ADL limitations (OR(95%CI)=11.15(3.43-36.23)). The multi-adjusted OR values tended to slightly decrease when covariates linked to medical burden were added to the model (model 1) as well as when past MDE and antidepressant use were further included (model 3) but not when socioeconomic status was added (model 2).

These results were not modified when the data from the phone interview were added as a sensitivity analysis to test the potential bias due to non-random dropout (321 additional time points at 7 years). The associations found in model 3 also remained significant when excluding the case of incident dementia (130 women and 78 men) except for severe DS and IADL in women (OR(95%CI)=1.50(0.86-2.60)). In men, Mild DS remained significantly

associated with IADL limitations (OR(95%CI)=4.31(1.85-10.06)) and in women Severe DS was still associated with social restriction (OR(95%CI)=1.99(1.04-3.80)) and ADL limitations (OR(95%CI)=7.47(1.81-30.84)).

No interactions were found between DS (mild or severe) and centre, past MDE or the number of chronic pathologies or cognitive, visual or hearing impairments, except in women for social restriction (p-value for interaction=0.04); depressed women with hearing impairment being at higher risk of confinement to home or neighbourhood (n=53, p=0.03) whereas the association with DS was not significant in those who were not hearing impaired (n=1685, p=0.42).

Among the 2377 subjects (1070 men and 1307 women) free of DS and of disability at baseline and with a 2-year depression evaluation, 27.1% of the men and 34.3% of the women had an increase in the CES-D score of at least three points over the first two years (χ^2 test, p=0.0002). The odds of having activity limitations associated with a 2-year increase in CES-D score was significantly higher in men and women for social restriction, mobility and IADL (**Table 5**). These associations were especially strong in men for social restriction and IADL with an OR (95%CI) equal to 3.43 (1.72-6.86) and 3.00 (1.72-5.24), respectively.

DISCUSSION

Gender differences in depression-related activity limitation risk

The most striking findings of this large study of community-dwelling elderly were that activity limitations risk varied according to DS severity and by sex. Women with Mild DS did not show increased risk in relation to any disability type, but those with severe DS were at higher risk of limitations in IADL, ADL and social restriction. On the other hand, men with Mild DS were at high risk of IADL limitations; an increased risk in social and mobility restriction was also found in an age-adjusted model, but this failed to reach significance in the multi-adjusted models. In men with Severe DS, we did not observe a significant association with any of the disability measures after 7 years of follow-up, probably due to lower number (4.9% compared to 12.2% for women) and a higher mortality rate. Indeed in the same cohort, an increase in depression-related 4-year mortality risk was observed in men with mild (OR=2.8) and treated severe DS (OR=5.3) whereas in women only non-treated severe DS which slightly increased risk (OR=1.8) (Ryan et al., 2008).

Several previous studies have reported an increase in activity limitations (most frequently severe ADL limitations) associated with DS in elderly community cohorts (see (Carriere et al., 2009; Schillerstrom et al., 2008), for reviews). Only two prospective studies have examined the impact of gender differences on severe level of disability (Barry et al., 2009; Dalle Carbonare et al., 2009). Dalle Carbonare et al observed an association between DS and short-term limitations in ADL for both gender and physical function disability for men (Dalle Carbonare et al., 2009). Barry et al using a 4-item ADL scale found an increased risk of experiencing severe disability associated with moderate and high levels of DS in men, and only with severe DS in women (Barry et al., 2009). We also observed an association between ADL and Severe DS in women. In men with Severe DS, the association tended to be

significant only in age-adjusted but not multi-adjusted model, probably due to a lack of power; few people being severely disabled in our sample.

Disability in relation to depression severity and gender differences

Our study is, we believe, the first to use several activity limitation scales in their validated forms. Mobility, IADL and ADL limitations correspond to an increased gradient of severity (Barberger-Gateau et al., 2000). Severe DS was predictive of multiple disabilities in women whereas the more likely consequence in men would be on mortality. Whereas ADL appears as an "ultimate" indicator of disability associated with Severe DS, IADL appears to be a more sensitive marker of disability as a function of depression severity level in our sample. Men with Mild DS were at very high risk of IADL disability (OR=5.07) whereas women even with Severe DS were at lower risk (OR=1.89). On the other hand, mobility limitations which correspond to a lower level of disability are probably not sufficiently sensitive to DS in this elderly sample (39.5% with such activity limitations at baseline). Mobility limitations were observed in people without DS at baseline but showing an early slight deterioration in CES-D score during follow-up. This was also the case for social restriction and IADL. We observed a slight gender difference in mobility and social restriction and a notable difference in IADL, men being at higher risk of disability. Our study thus gives an indication of the dynamics of the evolution of activity limitations at increasing levels of DS severity; different patterns of disability evolution possibly explaining gender differences. Some authors have distinguished subjects who rapidly develop severe disability (in less than one year - also called catastrophic disability) from those who develop severe disability for a longer period (progressive or insidious disability) (Ferrucci et al., 1996; Gill et al., 2004; Gill et al., 2010). Catastrophic disability could be the consequence of precipitating events such as stroke, hip fracture, cancer while progressive disability is more likely to be related to the frailty syndrome defined as an

aggregate of subclinical losses of reserve across multiple physiologic systems (Bortz, 2002; Fried et al., 2001) or insidious onset of cognitive deterioration. Both time spent in disability and time before death are shorter in men (Deeg et al., 2002; Peres and Jagger, 2005) indicating that men may be more vulnerable to catastrophic disability whereas women are at greater risk of an insidious progression with longer time spent in states of severe disability. Our results suggest that moderate DS could contribute to more rapid disability progression in men while in women severe DS is associated with slower progression.

Mechanisms potentially involved in the association between depression and disability

The mechanisms by which depression may generate activity limitation are not fully understood and may involve a combination of factors including physical comorbidity, cognitive and sensorial impairment, health behaviours, and biological factors. Vascular comorbidity is of particular importance in this context as it has been reported to be associated with functional decline (Wang et al., 2002). Depression could be an intermediate state between cerebral vascular disease and disability (Alexopoulos et al., 1997; Schillerstrom et al., 2008). We however, controlled for hypertension, diabetes, stroke, and cardiovascular disease and the association remained significant, suggesting that this pathway does not fully explain the association.

The early symptoms of cognitive decline are often destabilising and may also induce a depressive state. Inversely depression is associated with apathy and impaired cognitive functioning. The relationships persisted even after adjusting for baseline cognitive level and there was no significant interaction between cognitive impairment and depression in our study. Mehta et al (Mehta et al., 2002) found that in elderly people without ADL limitations, but not in those with ADL limitations at baseline, cognitive impairment and DS were both

risk factors for functional decline. In a sample of vulnerable elders eligible for nursing home care, Li et al (Li and Conwell, 2009) found that cognitive decline was associated with more elevated IADL scores when depression status worsened, but this was not observed for ADL scores. The strength of the interaction between DS and cognition probably depends on both cognitive level and degree of disability within the study population. A relatively small proportion of the participants in our study were at high risk for dementia (4.2% had baseline MMSE <24) which may explain the lack of interaction.

Sensory impairments, have been demonstrated to be a predictor of both onset and persistence of depression and functional disability (Chou, 2008; Crews and Campbell, 2004; Owsley et al., 2007). In our analysis, the relationship persisted after adjustment for both visual and hearing impairment. However, the assessment of hearing impairment was self-reported and the adjustment may not be complete considering that sensory impairments are often unrecognized by elderly people due to their slow progression.

Several behavioural mechanisms could also explain the disability risk associated with depression including impaired motivation and lower treatment compliance (Ciechanowski et al., 2000; Vinkers et al., 2004). Men in particular are likely to behave in ways which are detrimental to their overall health (Ciechanowski et al., 2000), however, the associations persisted even after controlling for comorbidity and "self-care" variables (*i.e.* smoking, alcohol, BMI, and level of visual and hearing impairment). More subjective factors such as impairment in affect regulation, social perception and greater tendency to amplify physical symptoms (Ormel et al., 1994) may also have played a role. Finally, dysfunctioning in the hypothalamic-pituitary-adrenal and sympathetic axes and immune system may also be involved (Katon et al., 2003).

Limitations

The data concerning disability outcomes were self-reported which may have led to over-reporting in depressed participants. Bias could also be introduced by the exclusion of participants with missing baseline data or lost to follow-up, who were more likely to be depressed, disabled or to have died. A difference in the attrition of our cohort was observed, men with DS being more often lost to follow-up (31.4% of depressed men and 14.9% of depressed women died during follow-up, 57.9% of depressed men and 48.5% of depressed women had less than 4 examinations). Men with DS may thus be censored before becoming disabled, so that associations between depression and disability were underestimated. However, the same results were obtained when data from telephone interviews of non-respondents were included (data not shown). Finally, in our study, we had no information regarding level of pain and its association with depression (Lin et al., 2003) which may have increased the risk of over-adjustment. We did, however, adjust for chronic pathologies commonly associated with pain, and this did not modify the associations.

Strengths

Our prospective study based on a large community sample permitted a dynamic evaluation of activity limitation with four evaluations over 7 years. We also used a number of validated scales exploring the major components of disability corresponding to distinct levels of disability severity. Depression was assessed using two distinct measures validated in the general population, including a structured diagnostic interview (Radloff, 1977; Sheehan et al., 1998), thus minimizing exposure misclassification. We were able to cover a wide range of depression profiles, from sub-clinical symptoms to major depression, thus addressing the problem of the varying definitions of depression in previous research. We also evaluated the early impact of 2 year-DS deterioration on disability. We controlled for a large number of potentially confounding factors, particularly measures of physical health (comorbidity,

sensorial impairments, health behaviors), cognitive impairment, past MDE and antidepressant use (with the risk of over-adjusting) which only slightly affected the results.

In conclusion, our findings suggest that the relationship between DS and incident activity limitations in the elderly is gender-dependent and also varies according to symptom load. Findings from this study suggest an increased risk of disability in men, even at the level of sub-clinical depression. This also highlights the importance of early detection of depressive symptoms in general practice, associated with treatments adapted to severity level.

References

Alexopoulos, G.S., Meyers, B.S., Young, R.C., Campbell, S., Silbersweig, D., Charlson, M., 1997. 'Vascular depression' hypothesis. Archives of general psychiatry 54, 915-922.

Barberger-Gateau, P., Rainville, C., Letenneur, L., Dartigues, J.F., 2000. A hierarchical model of domains of disablement in the elderly: a longitudinal approach. Disabil Rehabil 22, 308-317.

Barry, L.C., Allore, H.G., Bruce, M.L., Gill, T.M., 2009. Longitudinal association between depressive symptoms and disability burden among older persons. Journal of Gerontology A 64, 1325-1332.

Blazer, D.G., 2003. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci 58, 249-265.

Bortz, W., 2002. A conceptual framework of frailty: a review. Journal of Gerontology A 57, M283-M288.

Carriere, I., Bouyer, J., 2002. Choosing marginal or random-effects models for longitudinal binary responses: application to self-reported disability among older persons. BMC Medical Research Methodology 2, 15.

Carriere, I., Villebrun, D., Peres, K., Stewart, R., Ritchie, K., Ancelin, M.L., 2009. Modelling complex pathways between late-life depression and disability: evidence for mediating and moderating factors. Psychological medicine 39, 1587-1590.

Chou, K.L., 2008. Combined effect of vision and hearing impairment on depression in older adults: evidence from the English Longitudinal Study of Ageing. Journal of affective disorders 106, 191-196.

Ciechanowski, P.S., Katon, W.J., Russo, J.E., 2000. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch. Intern. Med. 160, 3278-3285.

Crews, J.E., Campbell, V.A., 2004. Vision impairment and hearing loss among community-dwelling older Americans: implications for health and functioning. American Journal Public Health 94, 823-829.

Dalle Carbonare, L., Maggi, S., Noale, M., Giannini, S., Rozzini, R., Lo Cascio, V., Crepaldi, G., 2009. Physical disability and depressive symptomatology in an elderly population: a complex relationship. The Italian Longitudinal Study on Aging (ILSA). Am J Geriatr Psychiatry 17, 144-154.

Deeg, D.J., Portrait, F., Lindeboom, M., 2002. Health profiles and profile-specific health expectancies of older women and men: The Netherlands. Journal of women & aging 14, 27-46.

Ferrucci, L., Guralnik, J.M., Simonsick, E., Salive, M.E., Corti, C., Langlois, J., 1996. Progressive versus catastrophic disability: a longitudinal view of the disablement process. Journal of Gerontology A 51, M123-130.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189-198.

Fried, L., Tangen, C., Walston, J., Newman, A., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W., Burke, G., Mcburnie, M., 2001. Frailty in older adults: evidence for a phenotype. Journal of Gerontology A 56, M146-M156.

Gill, T.M., Allore, H., Holford, T.R., Guo, Z., 2004. The development of insidious disability in activities of daily living among community-living older persons. American Journal of Medicine 117, 484-491.

Gill, T.M., Gahbauer, E.A., Han, L., Allore, H.G., 2010. Trajectories of disability in the last year of life. The New England journal of medicine 362, 1173-1180.
ICF, 2001 International Classification of Functioning, Disability and Health. World Health Organization, Geneva, Switzerland
Katon, W.J., Lin, E., Russo, J., Unutzer, J., 2003. Increased medical costs of a population-based sample of depressed elderly patients. Archives of general psychiatry 60, 897-903.
Katz, S., Downs, T.D., Cash, H.R., Grotz, R.C., 1970. Progress in development of the index of ADL. Gerontologist 10, 20-30.
Kirsch, I., Deacon, B.J., Huedo-Medina, T.B., Scoboria, A., Moore, T.J., Johnson, B.T., 2008. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 5, e45.
Lawton, M.P., Brody, E.M., 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9, 179-186.
Li, L.W., Conwell, Y., 2009. Effects of changes in depressive symptoms and cognitive functioning on physical disability in home care elders. Journal of Gerontology A 64, 230-236.
Lin, E.H., Katon, W., Von Korff, M., Tang, L., Williams, J.W., Jr., Kroenke, K., Hunkeler, E., Harpole, L., Hegel, M., Arean, P., Hoffing, M., Della Penna, R., Langston, C., Unutzer, J., 2003. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. Journal of the American Medical Association 290, 2428-2429.
Lyness, J.M., Caine, E.D., King, D.A., Cox, C., Yoediono, Z., 1999. Psychiatric disorders in older primary care patients. J Gen Intern Med 14, 249-254.
Mehta, K.M., Yaffe, K., Covinsky, K.E., 2002. Cognitive impairment, depressive symptoms, and functional decline in older people. Journal of the American Geriatrics Society 50, 1045-1050.
Murray, C.J., Lopez, A.D., 1996. The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. In: Harvard School of Public Health (Ed.), Global Burden of Disease and Injury Series, vol. I. Haward University Press, Cambridge, MA, USA.
Ormel, J., VonKorff, M., Ustun, T.B., Pini, S., Korten, A., Oldehinkel, T., 1994. Common mental disorders and disability across cultures. Results from the WHO Collaborative Study on Psychological Problems in General Health Care. Journal of the American Medical Association 272, 1741-1748.
Owsley, C., McGwin, G., Jr., Scilley, K., Meek, G.C., Seker, D., Dyer, A., 2007. Effect of refractive error correction on health-related quality of life and depression in older nursing home residents. Archives of Ophthalmology 125, 1471-1477.
Peres, K., Jagger, C., 2005. Disability-free life expentancy of older French people: gender and education differentials from PAQUID cohort". European Journal of Ageing 2, 225-233.
Peres, K., Jagger, C., Matthews, F.E., 2008. Impact of late-life self-reported emotional problems on Disability-Free Life Expectancy: results from the MRC Cognitive Function and Ageing Study. International journal of geriatric psychiatry 23, 643-649.
Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M.R., Rahman, A., 2007. No health without mental health. Lancet 370, 859-877.
Radloff, L., 1977. The CES–D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1, 385-401.
Ritchie, K., Artero, S., Beluche, I., Ancelin, M.L., Mann, A., Dupuy, A.M., Malafosse, A., Boulenger, J.P., 2004. Prevalence of DSM-IV psychiatric disorder in the French elderly population. Br J Psychiatry 184, 147-152.

Rollman, B.L., Reynolds, C.F., 3rd, 1999. Minor and subsyndromal depression: functional disability worth treating. J Am Geriatr Soc 47, 757-758.

Rosow, I., Breslau, N., 1966. A Guttman health scale for the aged. J Gerontol B Psychol Sci Soc Sci 21, 556-559.

Ryan, J., Carriere, I., Ritchie, K., Stewart, R., Toulemonde, G., Dartigues, J.F., Tzourio, C., Ancelin, M.L., 2008. Late-life depression and mortality: influence of gender and antidepressant use. Br J Psychiatry 192, 12-18.

Schillerstrom, J.E., Royall, D.R., Palmer, R.F., 2008. Depression, disability and intermediate pathways: a review of longitudinal studies in elders. Journal of geriatric psychiatry and neurology 21, 183-197.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 59 Suppl 20, 22-33.

The 3C Study Group, 2003. Vascular factors and risk of dementia: Design of the three city study and baseline characteristics of the study population. Neuroepidemiology 22, 316-325.

Ustun, T.B., Ayuso-Mateos, J.L., Chatterji, S., Mathers, C., Murray, C.J., 2004. Global burden of depressive disorders in the year 2000. Br J Psychiatry 184, 386-392.

Vinkers, D.J., Stek, M.L., Gussekloo, J., Van Der Mast, R.C., Westendorp, R.G., 2004. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. Int. J. Geriatr. Psychiatry 19, 852-857.

Wang, L., van Belle, G., Kukull, W.B., Larson, E.B., 2002. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. Journal of the American Geriatrics Society 50, 1525-1534.

Acknowledgement

Funding: The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen-Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C-Study was also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, the Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon, the Fondation de France, the Ministry of Research-Inserm Programme 'Cohorts and collection of biological material' and Novartis. The Lille Genopole was supported by an unconditional grant from Eisai.

This work was carried out with the financial support of the "ANR - Agence Nationale de la Recherche - The French National Research Agency" under the "Programme National de Recherche en Alimentation et nutrition humaine", project "COGINUT ANR-06-PNRA-005" and under the "Programme Longévité et vieillissement", project 07-LVIE-004" and by The Institut de Recherche en Santé Publique (IReSP), Paris, France.

Role of funding source: the sponsors had no role in study design; in collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest: None.

Contributors. IC: study concept, statistical analyses and drafting of the manuscript, LAG: statistical analyses, KP, CB, PBG, KR, MLA: study concept and design, management of the cohort. All authors contributed to and approved the final version of the manuscript.

Table 1. Characteristics of the study population

	Men (n=1311)	Women (n=1880)	Chi2
	%	%	p
Age			
65-69	26.77	25.64	
70-74	36.92	34.36	0.21
75-80	24.26	26.70	
80+	12.05	13.30	
Education			
≤ 5 years	24.79	30.59	0.0003
Depressive symptomatology			
No	86.73	73.67	
Mild	8.39	14.15	<0.0001
Severe	4.88	12.18	
Past major depressive episode	8.54	19.57	<0.0001
Antidepressant treatment	3.66	9.15	<0.0001
Social restriction: home or neighbourhood confined	2.52	7.50	<0.0001
Activity limitations: Mobility	26.45	48.63	<0.0001
Activity limitations: IADL	4.59	7.96	0.0002
Activity limitations: ADL	0.31	0.37	0.99*
Incomes > 1500 €/month	79.56	57.55	<0.0001
Living alone	12.28	45.00	<0.0001

Alcohol			
0	7.40	24.73	
1-36 g/day	69.79	73.30	<0.0001
> 36g/day	22.81	1.97	
Smoking			
Never	30.97	80.64	
Former	60.26	15.80	<0.0001
Current	8.77	3.56	
BMI			
Normal	36.38	55.16	
Overweight	52.10	31.76	<0.0001
Obese	11.52	13.09	
Number of chronic pathologies			
None	26.80	34.15	
1-2	63.77	59.68	0.003
3-5	7.63	6.17	
Cognitive impairment	3.13	4.95	0.01
Visual impairment	10.30	16.97	<0.0001
Hearing impairment	4.81	3.19	0.02
HRT: current		12.98	

*Fisher's exact test

Table 2. Incident cases of disability by baseline depressive symptomatology and risk of disability adjusted for age, centre, time and time*age (model 0)

	Men					Women				
	Follow-up					Follow-up				
	2 years %	4 years %	7 years %	OR (95%CI)*	p-value	2 years %	4 years %	7 years %	OR (95%CI)*	p-value
Home or neighborhood confined										
Baseline DS	N=1214	N=1073	N=908	N=1276		N=1650	N=1519	N=1336	N=1738	
No	3.68	5.42	9.51	1		7.18	8.95	19.03	1	
Mild	5.15	9.64	14.75	2.71(1.01-7.26)	0.05	5.53	10.05	16.87	1.05(0.57-1.91)	0.88
Severe	6.90	2.04	8.11	3.85(1.05-14.04)	0.04	13.64	12.58	28.15	3.57(1.93-6.61)	<0.0001
Mobility: Rosow and Breslau										
Baseline DS	N=883	N=804	N=690	N=951		N=886	N=837	N=758	N=954	
No	30.20	34.87	41.19	1		40.65	49.93	53.83	1	
Mild	40.98	44.64	50.00	1.87(1.00-3.50)	0.05	45.63	61.96	42.86	1.34(0.87-2.07)	0.19
Severe	23.53	23.53	30.77	0.65(0.28-1.52)	0.32	55.56	51.52	47.27	1.45(0.88-2.39)	0.15
IADL										

Baseline DS	N=1179	N=1049	N=878	N=1245		N=1625	N=1502	N=1310	N=1723	
No	5.25	8.55	12.60	1		6.60	13.48	20.47	1	
Mild	10.31	19.32	28.13	5.20(2.37-11.38)	<0.0001	10.64	13.68	20.86	1.54(0.96-2.47)	0.08
Severe	5.56	6.12	11.11	1.95(0.62-6.16)	0.26	10.67	16.05	31.30	2.47(1.48-4.11)	0.0005
ADL										
Baseline DS	N=1234	N=1091	N=908	N=1303		N=1763	N=1621	N=1399	N=1864	
No	0.75	1.58	1.61	1		0.69	1.07	2.89	1	
Mild	0	3.33	6.25	3.15(0.62-15.92)	0.17	1.20	0.90	3.49	2.43(0.75-7.83)	0.14
Severe	1.69	2.00	2.63	6.55(0.84-50.88)	0.07	1.90	5.35	9.15	13.29(4.50-39.31)	<0.0001

DS: Depressive Symptomatology

Table 3: Multi-adjusted associations of baseline depressive symptomatology with disability incidence in men

	Model 1		Model 2		Model 3	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Home or neighborhood confined, N=1276						
No DS	1		1		1	
Mild DS	2.16(0.77-6.08)	0.14	2.29 (0.81-6.46)	0.12	2.22(0.80-6.13)	0.13
Severe DS	3.39(0.88-13.08)	0.08	3.57 (0.9-14.14)	0.07	2.17(0.51-9.2)	0.29
Mobility: Rosow and Breslau, N=951						
No DS					1	
Mild DS	1.68(0.9-3.12)	0.10	1.69 (0.91-4.49)	0.10	1.68(0.90-3.16)	0.11
Severe DS	0.6(0.26-1.39)	0.24	0.59 (0.25-1.36)	0.21	0.59(0.25-1.39)	0.23
IADL, N=1245						
No DS	1		1		1	
Mild DS	4.85(2.13-11.03)	0.0002	5.4 (2.38-12.24)	<0.0001	5.07(2.25-11.42)	<0.0001
Severe DS	1.78(0.54-5.87)	0.35	2.07 (0.62-6.94)	0.24	1.78(0.52-6.02)	0.36
ADL, N=1303						
No DS	1		1		1	

Mild DS	2.41(0.56-10.38)	0.24	2.16 (0.62-7.58)	0.23	2.09(0.60-7.24)	0.24
Severe DS	5.29(0.8-34.86)	0.08	4.78 (0.88-25.88)	0.07	3.82(0.68-21.39)	0.13

Model 1: adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment

Model 2: adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment, income, study level and, living alone

Model 3: adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment, income, study level, living alone, past major depressive episode and, antidepressant treatment.

DS: Depressive Symptomatology

Table 4: Multi-adjusted associations of baseline depressive symptomatology with disability incidence in women

	Model 1		Model 2		Model 3	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Home or neighborhood confined, N=1738						
No DS					1	
Mild DS	0.87(0.49-1.56)	0.64	0.88 (0.5-1.56)	0.66	0.82(0.46-1.46)	0.50
Severe DS	3.01(1.68-5.41)	0.0002	2.94 (1.65-5.24)	0.0003	2.36(1.31-4.25)	0.004
Mobility: Rosow and Breslau, N=954						
No DS					1	
Mild DS	1.33(0.86-2.04)	0.20	1.30 (0.84-2.00)	0.23	1.27(0.82-1.97)	0.28
Severe DS	1.48(0.9-2.43)	0.12	1.44 (0.87-2.38)	0.15	1.32(0.79-2.21)	0.29
IADL, N=1723						
No DS					1	
Mild DS	1.26(0.79-2.00)	0.34	1.35 (0.84-2.17)	0.22	1.26(0.78-2.02)	0.34
Severe DS	2.03(1.24-3.33)	0.005	2.22 (1.34-3.67)	0.002	1.89(1.13-3.15)	0.02
ADL, N=1864						

No DS	1		1		1	
Mild DS	2.17(0.68-6.89)	0.19	2.23 (0.68-7.30)	0.18	2.24(0.70-7.24)	0.18
Severe DS	11.18(3.93-31.86)	<.0001	12.1 (3.83-38.24)	<0.0001	11.15(3.43-36.23)	<0.0001

Model 1: adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment and, hormonal treatment

Model 2: adjusted for age, centre, time and time*age, , alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment, hormonal treatment, income, study level and, living alone

Model 3: adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment, hormonal treatment, income, study level, living alone, past major depressive episode and, antidepressant treatment.

DS: Depressive Symptomatology

Table 5: Adjusted associations of 2-year depressive deterioration (increase of 3 points or more at CES-D) with disability incidence in subjects free of depressive symptomatology at baseline

	Men		Women	
	OR (95%CI)*	p-value	OR (95%CI)*	p-value
Home or neighborhood confined	N=1049		N=1234	
	3.43 (1.72-6.86)	0.0005	2.76 (1.78-4.27)	<0.0001
Mobilty: Rosow and Breslau	N=794		N=725	
	2.18 (1.5-3.18)	<0.0001	1.68 (1.2-2.35)	0.003
IADL	N=1022		N=1214	
	3.00 (1.72-5.24)	0.0001	1.55 (1.03-2.34)	0.04
ADL	N=1065		N=1300	
	1.64 (0.67-4.03)	0.28	2.67 (0.95-7.53)	0.06

* adjusted for age, centre, time and time*age, alcohol, BMI, smoking, number of chronic pathologies, cognitive impairment, visual impairment, hearing impairment, hormonal treatment (women only), income, study level, living alone, past major depressive episode and, antidepressant treatment.