# Vision loss and 12-year risk of dementia in older adults: the 3C cohort study

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**ABSTRACT**

To analyze the longitudinal relationships between vision loss and the risk of dementia in the first 2 years, from 2 to 4 years and beyond 4 years) after inclusion and to determine the roles of depressive symptomatology and engagement in cognitively stimulating activities in these associations. This study is based on the Three-City (3C) study, a population-based cohort of 7736 initially dementia-free participants aged 65 years and over with 12 years of follow-up. Near visual impairment (VI) was measured and distance visual function (VF) loss was self-reported. Dementia was diagnosed and screened over the 12-year period. At baseline, 8.7% had mild near VI, 4.2% had moderate to severe near VI, and 5.3% had distance VF loss. Among the 882 dementia cases diagnosed over the 12-year follow-up period, 140 cases occurred in the first 2 years, 149 from 2 to 4 years and 593 beyond 4 years after inclusion. In Cox multivariate analysis, moderate to severe near VI was associated with an increased risk of dementia in the first 2 years (HR= 2.0, 95%CI: 1.2 to 3.3) and from 2 to 4 years (HR=1.8, 95%CI: 1.1 to 3.1) but the association was not significant beyond 4 years after inclusion even if pointing in similar direction (HR=1.3, 95%CI: 0.95 to 1.9). Mild near VI was associated with an increased risk of dementia only in the first 2 years (HR=1.6, 95%CI: 1.1 to 2.5). Moreover, self-reported distance VF loss was associated with an increased risk beyond 4 years after inclusion (HR= 1.5, 95%CI: 1.1 to 2.0) but the association was no longer significant after taking into account baseline cognitive performances. Further adjustment for engagement in cognitively stimulating activities only slightly decreased these associations. However, there was an interaction between vision loss and depressive symptomatology, with vision loss associated with dementia only among participants with depressive symptomatology. These results suggest that poor vision, in particular near vision loss, may represent an indicator of dementia risk at short and middle-term, mostly in depressed elderly people.

## INTRODUCTION

Vision loss (VL) is common in older adults and increases with age. The leading cause of VL is uncorrected refractive error [1], easily avoidable with corrective eyeglasses, lenses or refractive surgery. VL has been associated with cognitive impairment, but mainly in cross-sectional studies [2–10], whereas longitudinal studies have shown conflicting results [11–16]. Furthermore, little is known about the longitudinal association between VL and dementia, with only one previous study among participants aged 71 and older, showing that those who perceived that their vision was good or excellent had a lower risk of developing dementia [17].

Several hypotheses have been proposed to explain the association between VL and cognitive impairment: 1) VL may act through factors known to be associated with cognitive decline and dementia, in particular engagement in activities and depression [18–20]. Thus, VL may decrease the engagement in cognitively stimulating activities or participation in social life or increase the risk of depression, which may subsequently increase the risk of dementia [21–26]. 2) A lack of adequate sensory input could lead to neuronal atrophy and thus cognitive impairment [27]. 3) Visually impaired people may need to allocate more resources to perceive and interpret sensory information and thus have fewer resources for other cognitive tasks [28]. 4) Alternatively, VL and dementia may share common risk factors as aging [27]. 5) Finally, vision loss may be one of the early symptoms of dementia as, Alzheimer's disease (AD), the major cause of dementia, can affect the visual pathway and result in visual deficits [29].

In the present study, we aimed to investigate the longitudinal association between vision loss and the incidence of dementia. In particular, thanks to a 12-year follow-up period within a large population-based cohort we aimed to study the associations for several periods of time after inclusion. Moreover, we aimed to explore the roles of depressive symptomatology and engagement in cognitively stimulating activities in these associations.

## METHODS

This study forms part of the SENSE-Cog multi-phase research program, funded by the European Union Horizon 2020 program. SENSE-Cog aims to promote mental well-being in older adults with sensory and cognitive impairments (http://www.sense-cog.eu/). The first part of this project aims to better understand the links between sensory, cognitive and mental health in older Europeans.

### Study population

This study was based on the Three-City study (3C), a French population-based cohort of 9294 community-dwelling older adults aged 65 years and over who enrolled between 1999 and 2001. The aim of 3C is to assess the risk of dementia and cognitive decline due to vascular risk factors. The methodology of the 3C study has been described elsewhere [30]. Briefly, participants were recruited from the electoral rolls of three French cities: Bordeaux (n=2104), Dijon (n=4931) and Montpellier (n=2259). Data were collected during face-to-face interviews; trained neuropsychologists administered standardized questionnaires and performed clinical examinations at baseline and 2, 4, 7, 10 and 12 years later. Sociodemographic characteristics, lifestyle, cardiovascular risk factors, vision, and depressive symptomatology were assessed at each interview. A complete functional and cognitive evaluation with systematic screening for dementia was also conducted. Moreover, blood samples and participation in leisure activities were collected at baseline.

Among the 8250 participants who were without prevalent dementia at baseline and were followed up at least once during the 12-year follow-up period, 7736 had baseline data for both distance and near vision loss and were thus, included in this study (Figure 1).

### Diagnosis of dementia

Dementia was actively diagnosed at baseline and at each follow-up visit using a 3-step procedure. The first step consisted of a cognitive evaluation made by the neuropsychologist through a series of psychometric tests including at a minimum the MMSE [31], the Isaacs set test and the Benton Visual Retention Test [32,33]. Participants suspected of having dementia, based on either their neuropsychological performance or decline relative to a previous examination, were then examined by a senior neurologist to establish a clinical diagnosis. Finally, an independent committee of neurologists and geriatricians reviewed all potential cases of dementia with all available information in order to obtain a consensus on the diagnosis and etiology, according to the DSM-IV and the NINCDS-ADRDA criteria [34,35].

### Vision loss

Binocular near visual acuity was assessed using the Parinaud scale (a Jaeger-like reading test commonly used in France). Assessments were carried out using presenting vision with usual optical correction (i.e., their personal spectacles) where applicable, with a standardized reading distance of 33 cm. Mild near visual impairment (VI) was classified by Parinaud 3 or 4 (Snellen equivalent 20/30-20/60) and moderate to severe near VI by Parinaud > 4 (Snellen equivalent < 20/60). Distance visual function (VF) loss was self-reported, defined as an inability or difficulty in recognizing a familiar face at 4 meters, using presenting optical correction if any.

Leisure activities

Leisure activities were assessed at baseline using two different self-administered questionnaires. In Bordeaux, 28 activities were assessed, 12 of which were considered cognitively stimulating activities: going to the cinema, painting, sculpting, going to the theater, reading literature, reading newspapers, acting as a director of an association (sporting, cultural or political), playing board games, doing crossword puzzles, and travelling. One point was awarded for each activity performed [36]. In Dijon and Montpellier, 6 cognitively stimulating activities were considered among 19 activities assessed: reading, doing crossword puzzles, playing cards, going to the cinema/theater, practicing an artistic activity and managing an association (sporting, cultural or political). Participants were asked about the monthly frequency (0= never or rarely; 1= 1-3 per month; 2= 1 per week; 3= ≥2 per week) that they engaged in each activity, except for reading, for which participants were asked about the daily frequency (0= <1 hour per day; 1= 1-2 hours per day; 2= >2 hours per day). Cognitively stimulating activities scores were calculated by summing the item scores [37]. Due to the difference in assessments between the centers, cognitively stimulating activities scores were standardized (Z-score) for the analyses.

Depressive symptomatology

Depressive symptomatology at baseline was evaluated using the Center for Epidemiologic Studies Depression Scale (CESD) questionnaire, a 20-item self-report rating scale designed to evaluate the frequency of depressive symptoms experienced over the past week. Each item is scored from 0 (rarely) to 3 (most of the time). Thus, the total CESD score ranges from 0 to 60, increasing with the level of severity of depressive symptomatology. As previously validated, scored of ≥17 for men and ≥23 for women were used to define depressive symptomatology [38,39].

Potential confounders

The following sociodemographic factors were considered: age, gender, educational level (elementary school without diploma, short secondary school and higher levels), living alone and monthly income (<1500€, 1500-2300€, >€2300,

refusal to answer). As other sensory impairments may also have an impact on dementia risk [40], self-reported hearing loss, classified in three categories (no, mild and moderate to severe) was also considered. Other potential confounders included cardiovascular risk factors: hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg using the mean of two measures and/or antihypertensive medication), history of cardiovascular ischemic disease, history of stroke, hypercholesterolemia (cholesterol ≥6.20 mmol/L and/or hypolipemiant treatment), hypertriglyceridemia (triglycerides ≥1.7 mmol/L), diabetes (normal, hyperglycemia (fasting glycemia [6.1-7.0[ mmol/L, diabetes (fasting glycemia ≥7.0 mmol/L and/or antidiabetic treatment)), smoking habits (never, former, current), and body mass index (BMI) (weight/height$^2$) in four categories (<21, 27–29.9, ≥30 vs 21–26.9). Additionally, APOE genotype (at least one ε4 allele vs no ε4) was also taken into account.

Statistical analysis

Cox proportional hazards models with delayed entry (using age as time-scale) were used to compare the baseline characteristics of participants according to incident dementia and to estimate the risk of dementia associated with vision loss, providing hazard ratios (HR) and 95% confidence intervals (CI). For participants who developed dementia, time of event was determined at the middle of the interval between the visit when dementia was diagnosed and the last visit prior to dementia diagnosis. Participants who did not develop dementia were censored at the last follow-up visit. Near and distance vision loss were analyzed in separate models. In order to assess whether vision loss had a constant effect over time, vision loss was modelled by a time-dependent variable represented by a step function. The effects of vision loss on the risk of dementia were estimated in the first 2 years, from 2 to 4 years and beyond 4 years after inclusion. Supplementary analysis using other periods of time (the first 4 years, from 4 to 7 years and beyond 7 years after inclusion) was also performed. The multivariate model included the following covariates: center, gender, educational level, self-reported hearing loss, living alone, income, cardiovascular risk factors and ApoE4 genotype. A total of 276 participants had missing data for at least one covariate. To avoid excluding these participants and limit thus selection bias we performed multiple imputation for missing values [41].
To further assess the robustness of our analyses to potential reverse causation, we carried out a sensitivity analysis additionally adjusted for baseline cognitive status. A z-score of global cognition at baseline was computed, including performances on the MMSE, Isaacs Set Test and Benton Visual Retention Test.

We further studied the effects of engagement in cognitively stimulating activities and depressive symptomatology on the relationships between vision and dementia, these two factors being potentially associated with both vision and dementia. We first searched for a potential interaction between these two factors and vision loss on the risk of dementia

and then presented accordingly either adjusted or stratified analyses. The analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Study sample

At baseline, the mean age of the 7736 participants was 73.9 years; 61.3% were women, 39.5% had a high educational level, and 12.6% had depressive symptomatology (Table 1). The mean MMSE score was 27.4 (SD 1.9). A total of 882 participants developed dementia over the 12-year follow-up period (median= 9.1 years, range= 0.6 – 13.5) with an incidence of 14.5 cases per 1000 person-years. Participants who ultimately developed dementia were older, less educated, had lower income, more self-reported hearing loss, more vascular risk factors, more depressive symptomatology, reported less engagement in cognitively stimulating activities, were more often APOE4 carriers and had lower MMSE scores at baseline. They had also more often near VI and distance VF loss.

### Vision loss and risk of incident dementia

- *Main analysis*

Among the 7736 participants, 671 (8.7%) had mild near VI, 325 (4.2%) moderate to severe near VI and 413 (5.3%) distance VF loss. Among the 882 cases of dementia occurred over the 12-year follow-up, 140 cases occurred before the first follow-up time ( in the first 2 years), 149 between the first and the second follow-up time ( from 2 to 4 years) and 593 after the second follow-up time (beyond 4 years). In the analyses adjusted for all the potential confounders (Table 2), mild near VI was associated with an increased risk of dementia only in the first 2 years (HR=1.6, 95%CI: 1.1 to 2.5). Moderate to severe near VI was associated with an increased risk of dementia in the first 2 years (HR= 2.0, 95%CI: 1.2 to 3.3) and from 2 to 4 years (HR=1.8, 95%CI: 1.1 to 3.1), but the risk was not significantly increased beyond 4 years although there was a trend (HR= 1.3, 95%CI: 0.95 to 1.9). Distance VF loss was associated with an increased risk of dementia only beyond 4 years (HR= 1.5, 95%CI: 1.1 to 2.0). In sensitivity analysis additionally adjusted for baseline global cognition, results were almost unchanged for near vision although the association between mild near VI and dementia in the first 2 years was no longer significant (Supplementary table 1, HR=1.5, 95%CI: 0.98 to 2.4, p=0.06). However, distance VF loss was no longer significantly associated with dementia beyond 4 years (HR= 1.3, 95%CI: 0.94 to 1.8). In the supplementary analysis using other cut-offs (<4 years, 4-7 years and ≥7 years) we found a significant effect of vision loss on dementia for moderate to severe near VI only in the first 4 years after inclusion (HR=1.88,

95%CI 1.29;2.73, p=0.001); after 7 years the increased risk associated with distance VF loss was only borderline significant (HR=1.55, 95%CI 0.99;2.44, p=0.055) (Supplementary table 2).

- *Engagement in cognitively stimulating activities*

There was no interaction between vision loss and cognitively stimulating activities, thus to analyze the effects of engagement in cognitively stimulating activities on the associations between vision loss and dementia we additionally adjusted for these activities. Engagement in cognitively stimulating activities was evaluated for 7089 participants, this relatively large number of missing data (8.4%) being due to the evaluation by self-questionnaire. At baseline, participants with near VI had lower mean scores of engagement in cognitively stimulating activities, with scores decreasing as the severity of VI increased (0.08 (95% CI: 0.06 to 0.11) for no near VI, -0.14 (95% CI: -0.22 to -0.06) for mild VI, -0.38 (95% CI:-0.49 to -0.26)for moderate to severe VI, p<0.0001 adjusted for age). After additional adjustment for these activities in the multivariate model (Table 3, model B), mild near VI was still associated with an increased risk of dementia in the first 2 years (HR=1.7, 95%CI: 1.0 to 2.8). Moderate to severe near VI was also associated with an increased risk of dementia from 2 to 4 years (HR=1.8, 95%CI: 1.1 to 3.3) but the risk was no longer significant beyond 4 years (HR=1.7, 95%CI: 0.9 to 3.2). As in the previous model distance VF loss was associated with an increased risk only beyond 4 years (HR=1.4, 95%CI 1.0 to 2.0). Compared to results observed in the same sample (Table 3, Model A), HRs were only slightly decreased after this adjustment for cognitively stimulating activities.

- *Depressive symptomatology*

Analyses stratified on depressive symptomatology showed an interaction between depressive symptomatology and vision loss. At baseline, distribution of depressive symptomatology differed according to near VI (p=0.0040): participants with moderate to severe near VI had more often depressive symptomatology (15.6% (95%CI; 11.7 to 20.1) vs 12.4% (95%CI: 11.6 to 13.2) for those without near VI) and had a higher proportion of missing evaluations of their depressive symptomatology (5.2% (95% CI: 3.1 to 8.2) vs 2.1% (95%CI: 1.8 to 2.5)). Among the 6610 participants without depressive symptoms at baseline, 700 developed a dementia over the follow-up compared to 150 of the 951 participants with depressive symptoms. The risks of dementia associated with visual loss were significantly increased only among participants with depressive symptomatology and not in those without. Indeed, moderate to severe near VI was associated with an increased risk in the first 2 years (HR=2.9. 95%CI 1.0 to 7.9) and beyond 4 years (HR=3.1, 95%CI 1.5 to 6.5); the risk from 2 to 4 years tended to be increased but not significantly (HR=2.6, 95%CI 0.9 to 7.9). Distance VF loss was associated with an increased risk of dementia only beyond 4 years (HR=2.8, 95%CI 1.5 to 5.3).

## DISCUSSION

Within a large population-based cohort followed up over 12 years, we found that moderate to severe near VI was associated with an increased risk of dementia in the first 2 years and from 2 to 4 years after adjusting for multiple potential confounders, whereas mild near VI was associated with dementia only in the first 2 years. Less engagement in cognitively stimulating activities only slightly decreased these associations. However, stratified analyses on depressive symptomatology showed an interaction between vision loss and depressive symptomatology, such that moderate to severe near visually impaired participants had an increased risk of dementia in the first 2 years, from 2 to 4 years (at the limits of the significance) and beyond 4 years only when depressive symptomatology was present, with a nearly three-fold increased risk. Participants self-reporting distance VF loss had an increased risk of dementia only beyond 4 years, but that association was no longer significant after taking into account baseline cognitive performances.

Most of the previous research in this area has focused on cognition rather than dementia [2–16]. Within cross-sectional studies, the results show either a significant association between VI and cognition [2–8] or no association [9,10]. In longitudinal studies, significant associations between VI and cognitive decline have been found [12,14–16], using different assessments of VI, either a measure of contrast sensitivity[12], a measure of presenting near VA [14] or presenting distance VA [16] or self-reported decline in near or distance vision [15]. Regarding distance vision, however, other studies using measures of presenting distance VA [14] or best-corrected distance VA [11,13] have not found any association, or they found an association only when decline in distance vision was considered [13]. However, the cognitive tests have differed between studies, with some including items requiring vision [12,15,16] whereas others have used blind versions of cognitive tests [11,14]. Only one study presented results according to several cognitive tests. The authors found significant associations between measured decline in distance vision and several cognitive tests exploring speed, executive functions and memory, but all of them required visual capacities. In contrast, there was no association with the only test not requiring vision, i.e., the verbal fluency test [13].

In addition, to our knowledge, only one study has explored the longitudinal association between VL and risk of dementia [17], focusing only on self-reported VL without exploring the potential factors involved in that association. In this American retrospective study on 625 older adults aged 71 years and older, who were followed up over 8.5 years, the authors found that participants who reported their corrected (if applicable) vision as good or excellent at baseline had a reduced 63% risk of dementia after adjusting for potential confounders. However, there was no indication about the kind of vision (near or distance) studied and the authors did not evaluate the effect of vision loss on dementia risk over time.

Several hypotheses have been proposed to explain the association between vision and dementia, either in favor of a direct role of VL or via confounding factors, measurement bias and common processes [27,28]. To limit the impact of potential confounders, we adjusted for numerous factors, including age, socio-economic factors, hearing impairment and vascular factors. Although residual confounds cannot be totally excluded, none of these adjustments explained the association. Moreover, as previous authors suggested that VL could be one of the first symptoms of dementia [42], we adjusted for baseline cognitive performance, and we assessed whether vision loss had a constant effect over time, by modeling the effect of vision loss on the risk of dementia in the first 2 years, from 2 to 4 years and beyond 4 years after inclusion. The risk of dementia associated with near vision loss was indeed higher in the two first periods than beyond 4 years. Thus, reverse causation cannot be excluded and some participants were probably in a pre-dementia phase with their visual impairment being one of the symptoms of this pre-dementia phase. However, although not significant, there was a trend to an association between near vision loss and dementia beyond 4 years in the main analysis. Moreover, near vision loss was associated with a significantly increased risk beyond 4 years among participants with depressive symptoms, with a three-fold increased risk. In addition, distance VF loss tended also to be associated with an increased risk beyond 4 years, suggesting that vision loss could be a risk factor of dementia.

Previous studies have also suggested that the effect of VL on dementia may be achieved through intermediate factors, in particular decreased engagement in cognitively stimulating activities [22,25] or an increased level of depressive symptomatology [23,24]. In our population, in spite of decreased engagement in cognitively stimulating activities by participants with near VI, taking into account these activities only slightly explained the association between near VI and dementia. We cannot exclude that the measurement of activities was not accurate enough or occurred not timely in the relationship between VI and dementia, but it seems not to be the main factor involved. On the contrary, depressive symptomatology seems to be particularly involved in the relationship between vision loss and dementia. Indeed, an interaction between vision loss and depressive symptomatology was found with a risk of dementia for visually impaired participants significantly increased only for those with depressive symptomatology. As such, VL could worsen the risk of dementia in participants with pre-existing depressive symptoms. The mechanisms of this interaction need to be further explored to understand if there are potential underlying pathophysiological mechanisms, or if it acts through environmental or social factors, for example, social isolation and its consequences on recourse to care. Moreover, whether depression is a risk factor or a prodromal symptom of dementia is still unknown [43]. Thus, this increased risk of dementia in participants with vision loss and depressive symptoms could also reflect at least partly the onset of dementia more so than a real increased risk. Furthermore, the direction of the relation between visual impairment and

241 depression is still uncertain, but previous papers from the 3C-Study showed an increased risk of depressive
242 symptomatology or suicidal ideation in participants with visual loss ([23,44]).
243 Our results have some limitations. Even after attempting to explore possible factors involved and in spite of a
244 longitudinal design with 12 years of follow-up, the temporal sequence between visual loss, engagement in cognitively
245 stimulating activities and depression is difficult to evaluate. Indeed, all of these factors can change over time. Moreover,
246 distance vision was self-reported using a single question; thus, it is less accurate than other standard measures. Indeed,
247 the meaning of 4-meters distance is really difficult to estimate and may vary from one participant to another. Moreover
248 self-reported ability of vision loss probably varies according to cognitive capacities. However, surprisingly the
249 association between distance VF loss and dementia was observed only beyond 4 years, even if it was no longer
250 significant after adjustment for global cognition. For near vision, the test used (the Parinaud chart) required the ability
251 to read, which can potentially be impaired in cognitive impairment. However, the association between near VI and
252 dementia remained after additionally adjusting for baseline cognition. In addition, other parameters of vision, such as
253 contrast sensitivity or visual field, are probably important to study but were not available in our study. Moreover, we
254 did not have information about best-corrected visual acuity neither about the cause of the decreased near vision loss,
255 which could be due to under corrected refractive error or eye-diseases such as glaucoma or age-related macular
256 degeneration. Indeed, some studies have suggested that dementia and some eye diseases could share common age-
257 related pathogenesis [45]. However, our objective was to study the association between vision loss (evaluated with
258 visual acuity used in daily life) and dementia, whatever the cause of vision loss. Beyond clinical diagnosis of dementia,
259 it would be of great interest to document whether vision loss is associated with imaging markers of Alzheimer's disease
260 and dementia. Within a subsample of the 3C-Bordeaux participants we failed to find a cross-sectional association
261 between vision loss and hippocampus volume. However, these analyses deserve to be further explored and replicated on
262 a larger sample. Finally, engagement in cognitively stimulating activities was assessed using self-administered
263 questionnaires, with some missing data. As expected, the participants answering the questionnaire were younger, more
264 educated, had less cardiovascular risk factors and better cognition at baseline. However, the associations were almost
265 unchanged in this subsample.
266 The strengths of our results are attributable to a large population-based cohort with a long period of follow-up, a
267 baseline measure of presenting binocular near visual acuity using a standardized scale and an adjustment for numerous
268 major potential confounding factors. Moreover, we actively screened for dementia using validation by an independent
269 committee. We explored factors – namely, depressive symptomatology and engagement in cognitively stimulating

activities – that may be involved in the association between VL and risk of dementia. Finally, we assessed the effect of vision loss on dementia over time.

Conclusions

This longitudinal population-based study suggests that moderate to severe near VI could represent an indicator of dementia risk in the subsequent years, particularly in people suffering from depression. These results need to be replicated in other large longitudinal studies with both measure of near and distance visual acuity, and potential mediators need to be further explored. A large part of VL is correctable or preventable [46] . However, future researches and interventional studies are needed to further evaluate whether VL is only an indicator of future dementia or whether the improvement of VL, may represent a promising opportunity for dementia prevention.

## COMPLIANCE WITH ETHICAL STANDARDS

*Conflict of interest*

Authors V. Naël and AC Scherlen are Essilor International employees. Author C. Delcourt is a consultant for Bausch & Lomb, Novartis, and Laboratoires Théa and has received research grants from Laboratoires Théa. The authors K. Pérès, JF. Dartigues, L. Letenneur, H. Amieva, A. Arleo, I. Carrière, C. Tzourio, C. Berr and C. Helmer declare that they have no conflict of interest.

*Research involving Human Participants*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Kremlin-Bicêtre University Hospital and Sud-Mediterranée III committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

*Informed consent*

Informed consent was obtained from all individual participants included in the study.

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393 **Table 1. Baseline characteristics according to incident dementia over the 12-year follow-up: The Three-City (3C)**
394 **cohort study (n=7736)**

| | **Incident dementia** (n=882) | **No incident demented** (n=6854) | **P[a]** | **Total** |
|---|---|---|---|---|
| **Age, mean (SD)** | 76.9 (5.4) | 73.6 (5.3) | **<0.0001** | 73.9 (5.4) |
| **Gender: female** | 575 (65.2) | 4165 (60.8) | 0.9258 | 4740 (61.3) |
| **Educational level** | | | **<0.0001** | |
| Elementary school without diploma | 128 (14.6) | 461 (6.7) | | 589 (7.6) |
| Short secondary school | 446 (50.7) | 3642 (53.2) | | 4088 (52.9) |
| Higher level | 305 (34.7) | 2744 (40.1) | | 3049 (395) |
| **Living alone** | 367 (41.7) | 2372 (34.7) | 0.9044 | 2739 (35.5) |
| **Month income** | | | **<0.0001** | |
| <€1500 | 379 (46.5) | 2353 (36.5) | | 2642 (36.3) |
| €1500 - 2300 | 214 (26.3) | 1840 (28.5) | | 2054 (28.3) |
| >€2300 | 222 (27.2) | 2353 (36.5) | | 2575 (35.4) |
| **Depressive symptomatology** | | | **<0.0001** | |
| No | 700 (82.4) | 5910 (88.1) | | 6610 (87.4) |
| Yes | 150 (17.7) | 801 (11.9) | | 951 (12.6) |
| **Cognitively stimulating activities, mean (SD)[b]** | -0.21 (1.0) | 0.08 (1.0) | **<0.0001** | 0.05 (1.0) |
| **Smoking habits** | | | 0.5045 | |
| Never | 586 (66.6) | 4183 (61.0) | | 4769 (61.7) |
| Past smoker | 261 (29.7) | 2280 (33.3) | | 2541 (32.9) |
| Current smoker | 33 (3.8) | 390 (5.7) | | 423 (5.5) |
| **BMI** | | | 0.3880 | |

| | | | | |
|---|---|---|---|---|
| <21 | 100 (11.5) | 702 (10.3) | | 802 (10.4) |
| 21-26.9 | 484 (55.7) | 3861 (56.7) | | 4345 (56.6) |
| 27-29.9 | 172 (19.8) | 1338(19.6) | | 1510 (19.7) |
| ≥30 | 113 (13.0) | 910 (13.4) | | 1023 (13.3) |
| **Hypertension (>140/90)** | 700 (79.4) | 5262 (76.8) | 0.8041 | 5962 (77.1) |
| **History of stroke** | 40 (4.6) | 147 (2.2) | **<0.0001** | 187 (2.4) |
| **History of cardiovascular disease** | 74 (8.5) | 410 (6.0) | **0.0076** | 484 (6.3) |
| **Hypercholesterolemia** | | | 0.1644 | |
| No | 333 (40.4) | 2818 (42.3) | | 3151 (42.1) |
| Yes | 492 (59.6) | 3843 (57.7) | | 4335 (57.9) |
| **Hypertriglyceridemia** | | | **0.0030** | |
| No | 648 (80.3) | 5492 (83.6) | | 6140 (83.2) |
| Yes | 159 (19.7) | 1079 (16.4) | | 1238 (16.8) |
| **Diabetes** | | | **<0.0001** | |
| Normal glycemia | 651 (80.8) | 5750 (87.4) | | 6401 (86.7) |
| Hyperglycemia | 32 (4.0) | 241 (3.7) | | 273 (3.7) |
| Diabetes | 123 (15.3) | 589 (9.0) | | 712 (9.6) |
| **APOE4 carrier** | | | **<0.0001** | |
| No | 587 (73.1) | 5306 (80.9) | | 5893 (80.1) |
| Yes | 216 (26.9) | 1253 (19.1) | | 1469 (20.0) |
| **MMSE, mean (SD)** | 26.5 (2.1) | 27. 5 (1.9) | **<0.0001** | 27.4 (1.9) |
| **Hearing loss** | | | **0.0180** | |
| No | 485 (55.4) | 4288 (62.8) | | 4773 (61.9) |
| Mild | 299 (34.1) | 2080 (30.5) | | 2379 (30.9) |
| Moderate to severe | 92 (10.5) | 462 (6.8) | | 554 (7.2) |
| **Near visual impairment** | | | **<0.0001** | |

| | | | | |
|---|---|---|---|---|
| No (≥20/30) | 698 (79.1) | 6042 (88.2) | | 6740 (87.1) |
| Mild (20/30 – 20/60) | 115 (13.0) | 556 (8.1) | | 671 (8.7) |
| Moderate to severe (<20/60) | 69 (7.8) | 256 (3.7) | | 325 (4.2) |
| **Distance visual function loss** | 77 (8.7) | 336 (4.9) | **0.0014** | 413 (5.3) |

Abbreviations: BMI= Body Mass Index; MMSE= Mini-Mental State Examination; SD= Standard Deviation;

Missing data: educational level (n=10), living alone (n=18), income (n=465), depressive symptomatology (n=175), smoking (n=3), BMI (n=56), hypertension (n=1), stroke (n=81), hypercholesterolemia (n=250), hypertriglyceridemia (n=358), diabetes (n=350), APOE4 (n=374), MMSE (n=35), hearing loss (n=30), cognitively stimulating activities (n=647)

Unless otherwise indicated, data are expressed as n (%)

[a] Cox models for the risk of dementia with age used as the time-scale except for age, which was tested using a 2-tailed T test

[b] z-score

**Table 2. Risk of dementia by vision loss in the first 2 years, from 2 to 4 years and beyond 4 years after inclusion: The Three-City (3C) cohort study (n=7736)**

| | <2 years (n=698) | | | | 2-4 years (n=1311) | | | | ≥4 years (n=5727) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |
| **Near visual impairment** | 140 | | | | 149 | | | | 593 | | | |
| No | 96 | Ref | | | 113 | Ref | | | 489 | Ref | | |
| Mild | 27 | 1.63 | 1.06 – 2.51 | **0.027** | 20 | 1.15 | 0.71 – 1.86 | 0.57 | 68 | 1.00 | 0.77 – 1.31 | 0.99 |
| Moderate to severe | 17 | 1.95 | 1.16 – 3.28 | **0.012** | 16 | 1.82 | 1.07 – 3.08 | **0.027** | 36 | 1.34 | 0.95 – 1.89 | 0.095 |
| **Distance visual function loss[b]** | 13 | 1.12 | 0.63 – 1.99 | 0.70 | 14 | 1.22 | 0.70 – 2.13 | 0.48 | 50 | 1.49 | 1.11 – 2.00 | **0.008** |

Abbreviations: CI= Confidence Interval; HR= Hazard Ratio

[a] Adjusted for center, age, gender, educational level, for hearing loss, living alone, income, depressive symptomatology at baseline, smoking habits, body mass index, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes and APOE4 genotype

[b] Separate models

**Table 3. Risk of dementia by vision loss, with supplementary adjustment for engagement in cognitively stimulating activities: The Three-City (3C) cohort study (n=7089)**

| | <2 years (n=611) | | | | 2-4 years (n=1190) | | | | ≥4 years (n=5288) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model A without adjustment for cognitively stimulating activities[a.b]** | | | | | | | | | | | | |
| **Near visual impairment** | 107 | | | | 125 | | | | 518 | | | |
| No | 76 | Ref | | | 97 | Ref | | | 440 | Ref | | |
| Mild | 19 | 1.71 | 1.03 – 2.84 | **0.038** | 14 | 1.09 | 0.62 – 1.92 | 0.75 | 49 | 0.95 | 0.70 – 1.28 | 0.73 |
| Moderate to severe | 12 | 1.86 | 1.01 – 3.44 | **0.048** | 14 | 2.00 | 1.14 – 3.53 | **0.016** | 29 | 1.34 | 0.91 – 1.96 | 0.14 |
| **Distance visual function loss[c]** | 10 | 1.19 | 0.62 – 2.29 | 0.60 | 10 | 1.06 | 0.55 – 2.02 | 0.87 | 42 | 1.52 | 1.11 – 2.09 | **0.010** |
| **Model B + adjustment for cognitively stimulating activities[b]** | | | | | | | | | | | | |
| **Near visual impairment** | 107 | | | | 125 | | | | 518 | | | |
| No | 76 | Ref | | | 97 | Ref | | | 440 | Ref | | |
| Mild | 19 | 1.69 | 1.02 – 2.81 | **0.042** | 14 | 1.07 | 0.61 – 1.88 | 0.81 | 49 | 0.94 | 0.70 – 1.28 | 0.70 |
| Moderate to severe | 12 | 1.71 | 0.92 – 3.16 | 0.087 | 14 | 1.84 | 1.05 – 3.25 | **0.035** | 29 | 1.27 | 0.87 – 1.86 | 0.22 |
| **Distance visual function loss[c]** | 10 | 1.09 | 0.57 – 2.10 | 0.80 | 10 | 0.98 | 0.51 – 1.88 | 0.95 | 42 | 1.42 | 1.03 – 1.95 | **0.032** |

Abbreviations: CI= Confidence Interval; HR= Hazard Ratio

[a] Model re-run among participants without missing data on cognitively stimulating activities

[b] Model adjusted for center, age, gender, educational level, hearing loss, living alone, income, smoking habits, body mass index, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes and APOE4 genotype

[c] Separate models

**Table 4. Risk of dementia stratified by depressive symptomatology: The Three-City (3C) cohort study (n=7561)**

| | No depressive symptoms (n=6610) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <2 years (n=552) | | | | 2-4 years (n=1080) | | | | ≥4 years (n=4978) | | | |
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |
| **Near visual impairment** | 100 | | | | 113 | | | | 487 | | | |
| No | 71 | Ref | | | 86 | Ref | | | 406 | Ref | | |
| Mild | 20 | 1.62 | 0.98 – 2.68 | 0.06 | 16 | 1.18 | 0.69 – 2.03 | 0.54 | 58 | 1.02 | 0.76 – 1.36 | 0.90 |
| Moderate to severe | 9 | 1.48 | 0.73 – 2.97 | 0.28 | 11 | 1.70 | 0.90 – 3.20 | 0.10 | 23 | 1.07 | 0.70 – 1.63 | 0.77 |
| **Distance visual function loss[b]** | 6 | 0.80 | 0.35 – 1.83 | 0.60 | 10 | 1.26 | 0.66 – 2.42 | 0.49 | 35 | 1.25 | 0.88 – 1.77 | 0.22 |
| | **Depressive symptoms (n=951)** | | | | | | | | | | | |
| | <2 years (n=115) | | | | 2-4 years (n=193) | | | | ≥4 years (n=643) | | | |
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |
| **Near visual impairment** | 30 | | | | 28 | | | | 92 | | | |
| No | 19 | Ref | | | 21 | Ref | | | 73 | Ref | | |
| Mild | 6 | 2.11 | 0.83 – 5.39 | 0.12 | 3 | 1.07 | 0.31 – 3.63 | 0.92 | 10 | 1.18 | 0.59 – 2.37 | 0.65 |
| Moderate to severe | 5 | 2.87 | 1.04 – 7.94 | **0.04** | 4 | 2.62 | 0.87 – 7.89 | 0.087 | 9 | 3.07 | 1.46 – 6.47 | **0.003** |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Distance visual function loss[b]** | 4 | 1.09 | 0.37 – 3.17 | 0.88 | 4 | 1.29 | 0.44 – 3.83 | 0.64 | 13 | 2.83 | 1.52 – 5.28 | **0.001** |

Abbreviations: CI= Confidence Interval; HR= Hazard Ratio

[a] Adjusted for center, age, gender, educational level, for hearing loss, living alone, income, depressive symptomatology at baseline, smoking habits, body mass index, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes and APOE4 genotype
[b] Separate models

**Supplementary Table 1. Risk of dementia by vision loss in the first 2 years, from 2 to 4 years and beyond 4 years after inclusion with supplementary adjustment for baseline cognitive performance: The Three-City (3C) cohort study (n=7557)**

| | <2 years (n=672) | | | | 2-4 years (n=1282) | | | | ≥4 years (n=5603) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |
| **Near visual impairment[b]** | 135 | | | | 146 | | | | 568 | | | |
| No | 94 | Ref | | | 110 | Ref | | | 473 | Ref | | |
| Mild | 26 | 1.52 | 0.98 – 2.36 | 0.06 | 20 | 1.12 | 0.69 – 1.81 | 0.65 | 66 | 0.96 | 0.73 – 1.25 | 0.75 |
| Moderate to severe | 15 | 1.77 | 1.02 – 3.07 | **0.042** | 16 | 2.11 | 1.24 – 3.58 | **0.006** | 29 | 1.29 | 0.88 – 1.89 | 0.20 |
| **Distance visual function loss[b]** | 11 | 0.89 | 0.48 – 1.65 | 0.71 | 14 | 1.14 | 0.65 – 2.00 | 0.64 | 40 | 1.30 | 0.94 – 1.81 | 0.11 |

Abbreviations: HR= Hazard Ratio; CI= Confidence Interval

[a] Adjusted for center, age, gender, educational level, hearing loss, living alone, income, smoking habits, body mass index, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes, APOE4 genotype and baseline cognitive performance (computed as a Z-score based on Mini Mental State Examination, Isaacs Set Test and Benton Visual Retention Test)

[b] Separate models

**Supplementary Table 2. Risk of dementia by vision loss in the first 4 years, from 4 to 7 years and beyond 7 years after inclusion: The Three-City (3C) cohort study (n=7736)**

| | <4 years (n=2009) | | | | 4-7 years (n=902) | | | | ≥7 years (n=4825) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] | No of cases | HR | 95%CI | P[a] |
| **Near visual impairment** | 289 | | | | 331 | | | | 262 | | | |
| No | 209 | Ref | | | 276 | Ref | | | 213 | Ref | | |
| Mild | 47 | 1.38 | 1.00 – 1.91 | 0.0504 | 35 | 0.88 | 0.62 – 1.26 | 0.50 | 33 | 1.17 | 0.81 – 1.70 | 0.41 |
| Moderate to severe | 33 | 1.88 | 1.29 – 2.73 | **0.001** | 20 | 1.22 | 0.77 – 1.93 | 0.39 | 16 | 1.52 | 0.91 – 2.53 | 0.11 |
| **Distance visual function loss[b]** | 27 | 1.17 | 0.79 – 1.75 | 0.44 | 29 | 1.45 | 0.99 – 2.12 | 0.0597 | 21 | 1.55 | 0.99 – 2.44 | 0.0547 |

Abbreviations: CI= Confidence Interval; HR= Hazard Ratio

[a] Adjusted for center, age, gender, educational level, for hearing loss, living alone, income, depressive symptomatology at baseline, smoking habits, body mass index, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes and APOE4 genotype

[b] Separate models