Risk factors for late-onset generalized anxiety disorder: results from a 12-year prospective cohort (The ESPRIT study)

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Generalized anxiety disorder (GAD) is a chronic and highly prevalent disorder associated with increased disability and mortality in the elderly. Treatment is difficult with low rate of full remission, thus highlighting the need to identify early predictors for prevention in elderly people. The aim of this study is to identify and characterize incident GAD predictors in elderly people. A total of 1711 individuals aged 65 years and above and free of GAD at baseline were randomly recruited from electoral rolls between 1999 and 2001 (the prospective ESPRIT study). The participants were examined at baseline and five times over 12 years. GAD and psychiatric comorbidity were diagnosed with a standardized psychiatric examination, the Mini-International Neuropsychiatric Interview on the basis of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria and validated by a clinical panel. During the follow-up, 8.4% (95% confidence interval = 7.1–9.7%) of the participants experienced incident GAD, 80% being first episodes; the incident rate being 10 per 1000 person-years. The principal predictors of late-onset incident GAD over 12 years derived from a multivariate Cox model were being female, recent adverse life events, having chronic physical (respiratory disorders, arrhythmia and heart failure, dyslipidemia, cognitive impairment) and mental (depression, phobia and past GAD) health disorders. Poverty, parental loss or separation and low affective support during childhood, as well as history of mental problems in parents were also significantly and independently associated with incident GAD. GAD appears as a multifactorial stress-related affective disorder resulting from both proximal and distal risk factors, some of them being potentially modifiable by health care intervention.
MATERIALS AND METHODS

Participants

Community dwelling persons 65 years and over were recruited by random selection from the 15 electoral rolls of the Montpellier district between March 1999 and February 2001 as part of the prospective cohort ESPRIT study of late-life psychiatric disorder. Of the persons contacted, 72.7% accepted. Refusers were replaced by another subject drawn at random from the same electoral division such that each division is equally represented. Subjects refusing were slightly older and more likely to live alone than non-refusers. Each participant attended a half-day examination at inclusion and was re-examined with a detailed psychiatric interview on five further occasions at intervals of 2, 4, 7, 10 and 12 years. A flow chart is given as Supplementary Figure S1. Persons with dementia at baseline (n = 70) were excluded from the present study. Dementia was diagnosed by a neurologist as part of a standardized examination and validated by a panel of independent neurologists, as described previously. Of the 2189 dementia-free participants included in the ESPRIT study, 215 were excluded because of missing data on GAD at baseline and 91 because of prevalent GAD. Of this sample, 172 participants were missing all follow-up examinations (33 died; 55 were lost to follow-up and 84 had no GAD data). The population incidence rate was evaluated on 1711 participants with data available for at least one of the five follow-ups. A further 245 subjects with missing data on covariates (for example, waist-to-hip ratio (7.8%) and visual impairment (6.7%), see Table 1) were excluded from the multivariate analyses leaving 1466 subjects in the final sample. The study protocol was approved by the Ethics Committee of the University Hospital of Kremlin-Bicêtre and written informed consent was obtained from each participant.

Psychiatric disorder assessment

The diagnosis of lifetime anxiety disorder (GAD, social phobia, specific phobia and agoraphobia, panic disorder, obsessive compulsive disorder and PTSD) and major depression were performed by psychologists and psychiatric nurses according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria and using the MINI (Mini-International Neuropsychiatric Interview; French version 5.00), as described previously. The interviewers were initially trained for a 3-month period under the supervision of psychiatrists from the Department of Adult Psychiatry at Montpellier University Hospital. The MINI is a standardized and structured diagnostic examination validated within the general population setting, which uses a nonhierarchical case-identification procedure, thus permitting the diagnosis of psychiatric comorbidities. GAD was established using the current definition implying the presence of symptoms for at least 6 months. During the follow-up, MINI questions referred to the period since the previous examination, 2 or 3 years before. The positive cases were reviewed by a panel of independent psychiatrists as described previously.

Baseline socio-demographic, lifestyle, biological and clinical variables

The standardized interview included questions on socio-demographic characteristics (age, sex, education level (≥5 years)), smoking (current versus ever), alcohol consumption (≥12 g per day), diabetes (glycemia ≥ 7 mmol/l or treated), hypercholesterolemia (cholesterol ≥ 6.2 mmol/l or treated), hypertension (resting blood pressure ≥ 160/95 mm Hg or treated), measures of weight, height, waist and hip, as well as binary clinical variables, for example, respiratory disorders, osteoporosis, thyroid disorder, cancer, physical activity. Body mass index (expressed as kg/m²) and waist-to-hip ratio were calculated. Detailed medical questionnaires (with additional information from general practitioners) provided information on history of ischemic pathologies (angina, myocardial infarction, stroke, cardiovascular surgery and arteritis) and nonischemic cardiac pathologies (arrhythmia and heart failure). The participants were asked to show medical prescriptions, drug packages and any other relevant information to record all past-month somatic and psychotropic medications taken. Exposure to adverse life events in the past year was assessed using the TOSCA questionnaire. Mobility limitation, visual field impairments and other psychiatric disorders were determined as described. Venous blood samples were taken at baseline after 12-h fasting and lipid levels were measured. Global cognitive function was measured using the Mini-Mental State Examination and a score < 26 was considered to be indicative of cognitive impairment. Verbal fluency and visual memory were assessed by reference to Isaacs’ Set and the Benton Visual Retention Test, respectively. The Trail Making Tests A and B assessed psychomotor speed and executive function. Low cognitive performance was defined as scoring in the lowest tertile except for the timed Trail Making Test (highest).

Early environment

A self-report questionnaire (with binary yes/no response categories) examining traumatic experiences during childhood and adolescence was completed by 1365 of the 1604 participants (85.1%) at the second follow-up assessment by which time the study interviewers had established close relationships, facilitating the request for sensitive information. The subjects having not completed this questionnaire were more likely to have cognitive impairment and mobility limitation (P < 0.01) but did not differ regarding all the other characteristics including past GAD, incident GAD and other psychiatric disorders. It covered adverse exposure to severe abuse (physical, verbal or sexual abuse, neglect or excessive punishment), parental loss or separation, parents with mental disorder, alcohol or drugs problems, conflict at home, financial difficulties, excessive sharing of parental problems, war and natural catastrophe. Protective factors included parental affection, availability of an adult friend, having had a happy childhood or a normal education, parents perceived as doing their best, feeling happy at school and raised by both parents. Low affective support was defined as having reported less than six protective factors.

Statistical analysis

Prevalent GAD cases were excluded to avoid a methodological bias related to reverse causality (impossibility of separating cause and effect over time). Chi-square tests compared the characteristics of participants included in the analyses with those excluded. The incidence rate over the 12-year follow-up was calculated for 1711 participants with no prevalent GAD at baseline and with data available for at least one of the five follow-ups. For the calculation of the incidence rate, a participant is counted only once as a case, irrespective of the number of successive episodes (events) he/she may have experienced during the follow-up, and the date of onset corresponded to the first episode. The exact date of onset during the follow-up period being potentially imprecise or not known, onset was therefore considered to have occurred midway between the two examinations. Population incidence was estimated by dividing the number of new cases that occurred during the follow-up by the total number of GAD-free years lived by the cohort from baseline, expressed as number of new cases per 1000 person-years. A Cox model with delayed entry was used in the longitudinal analysis of incident GAD. The proportional-hazards assumptions were tested using Martingale residuals. Multivariate models included baseline covariates meeting Martingale residual criteria for proportionality of risk and associated with incident GAD in Cox models adjusted for sex (P < 0.15) and were reduced using a backward selection procedure keeping in the final model all the covariates significant at P < 0.15 (model 1). Model 2 was further adjusted for past GAD. These models were performed with the subjects having no missing data on any covariates included in the most complete model. Additional analyses were performed with the participants without a history of past GAD (‘first-onset cases’) as well as, separately in those termed as ‘recurrent’ that is with past GAD. SAS (version 9.3, SAS Institute, Cary, NC, USA) was used for the statistical analysis and all tests were two-tailed, and the significance level was P < 0.05.

RESULTS

Baseline characteristics of the sample

Of the 2189 non-demented participants in the ESPRIT study, 215 were excluded because of missing data on GAD at baseline, as well as 91 participants with prevalent GAD, and a further 172 (9.1%) had missing data for follow-up (see Supplementary Figure S1). Compared with the 1711 participants included in the longitudinal analysis, the 478 excluded participants were significantly older with a lower education level and more frequently having ischemic pathologies (P = 0.02), respiratory disorders (P = 0.004), thyroid disorder (P = 0.01), as well as cognitive impairment, depression, anxiety disorder and more frequent psychotropic medication use (P < 0.0001).
### Table 1. Incident cases of GAD over 12-year follow-up according to baseline variables

| Characteristic                              | Total N | No GAD, N = 1568 | Incident GAD, N = 143 | P* |
|---------------------------------------------|---------|------------------|-----------------------|----|
| **Age, years (mean, s.d.)**                 | 1711    | 72.6 (mean)      | 5.1 (s.d.)            |    |
| **Socio-demographic characteristics**       |         |                  |                       |    |
| Sex (female)                                | 1711    | 885              | 56.44                 |    |
| Living aloneb                               | 1708    | 412              | 26.33                 |    |
| Childless                                   | 1624    | 151              | 10.15                 |    |
| Education level (≥5 years)                  | 1710    | 777              | 49.59                 |    |
| **Lifestyle**                               |         |                  |                       |    |
| Alcohol consumption (≥12 g per day)         | 1681    | 623              | 40.45                 |    |
| Smoking (current or ever)                   | 1710    | 667              | 42.57                 |    |
| Physical activity                           | 1513    | 563              | 40.62                 |    |
| BMI (≥25 kg/m²)                             | 1701    | 724              | 46.41                 |    |
| WHR (≥0.94)                                 | 1578    | 313              | 21.72                 |    |
| **Lifetime adverse events**                 |         |                  |                       |    |
| Recent adverse events (≥1)                  | 1667    | 872              | 57.11                 |    |
| Parental loss or separation                 | 1365    | 154              | 12.33                 |    |
| Parents with mental problems               | 1365    | 225              | 18.01                 |    |
| Parents had problems with alcohol or drugs  | 1365    | 92               | 7.37                  |    |
| Conflict, nervous stress at homeb          | 1365    | 195              | 15.61                 |    |
| Poverty, financial difficulties             | 1365    | 275              | 22.02                 |    |
| Parents too often sharing their problems with children | 1365 | 164              | 13.13                 |    |
| Parent or adult friend affection            | 1365    | 1026             | 82.15                 |    |
| **Biological and clinical variables**       |         |                  |                       |    |
| LDL-cholesterol (≥4.01 mmol l⁻¹)            | 1688    | 500              | 32.30                 |    |
| HDL-cholesterol (≥1.73 mmol l⁻¹)            | 1698    | 1042             | 66.92                 |    |
| TG (≥0.95 mmol l⁻¹)                         | 1698    | 1050             | 67.44                 |    |
| Hypercholesterolemia (cholesterol ≥ 6.2 mmol l⁻¹ or treated) | 1702 | 863              | 55.32                 |    |
| Hypertension (resting blood pressure ≥160/95 mm Hg or treated) | 1711 | 695              | 44.32                 |    |
| Diabetes (glycemia ≥ 7 mmol l⁻¹ or treated) | 1697 | 134              | 8.61                  |    |
| Ischemic pathologies (≥1)                   | 1711    | 220              | 14.03                 |    |
| Arrhythmia and heart failure                | 1705    | 198              | 12.67                 |    |
| Respiratory disorders (dyspnea, asthma, or bronchitis) | 1711 | 73               | 4.66                  |    |
| Osteoporosis                                | 1696    | 273              | 17.54                 |    |
| Thyroid disorder                            | 1700    | 111              | 7.13                  |    |
| At least one chronic disorder              | 1711    | 973              | 62.05                 |    |
| MMSE (<26)#                                 | 1703    | 196              | 12.56                 |    |
| Iscaas Set test score (lowest tertile)      | 1682    | 394              | 25.52                 |    |
| Benton Visual Retention Test score (lowest tertile) | 1695 | 312              | 20.09                 |    |
| Trail Making Test A score (highest tertile) | 1686    | 419              | 27.12                 |    |
| Trail Making Test B score (highest tertile) | 1641    | 421              | 27.97                 |    |
| Visual impairment                           | 1597    | 88               | 6.02                  |    |
| Hearing impairment                          | 1703    | 64               | 4.10                  |    |
| Mobility limitation                         | 1705    | 59               | 3.78                  |    |
| Number of somatic medications ≥4           | 1711    | 698              | 44.52                 |    |

**Mental health**

- Use of psychotropic medication
  - 1711  186  11.86  26  18.18  0.03
- Major depression
  - 1698  24  1.54  10  7.04  0.0001
- Anxiety disorder (without GAD)
  - 1701  141  9.04  29  20.42  0.0003
- Phobia
  - 1702  133  8.53  27  18.88  0.001
- Posttraumatic stress disorder
  - 1711  2  0.13  1  0.70  NA¹
- Panic disorder
  - 1710  3  0.19  0  0.00  NA¹
- Obsessive compulsive disorder
  - 1711  6  0.38  1  0.70  NA¹
- Past GAD
  - 1711  85  5.42  29  20.28  0.0001

**Abbreviations:** BMI, body mass index; GAD, generalized anxiety disorder; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; TG, triglycerides; WHR, waist-to-hip ratio. *Cox model with delayed entry adjusted for age as time scale and sex (except when sex was examined). Variables not meeting Martingale residual criteria for proportionality of risk. At least one recent adverse event during the past year. Chronic disorders correspond to hypercholesterolemia, hypertension, diabetes, asthma, osteoporosis, thyroid disorder and recent cancer. Not applicable (NA) due to the low number of cases.
The baseline characteristics of the participants included in the analyses are shown in Table 1. The mean (s.d.) age was 72.6 (5.1) years with 58.4% women. The prevalence of major depression at baseline in the sample was 2.0% and that of phobia was 9.4%. PTSD and panic disorder each accounted for 0.2% and obsessive compulsive disorder for 0.4%. Psychotropic medication was taken by 12.4% of the participants, antidepressant for 7.2%; obsessive compulsive disorder for 0.4%; and antipsychotics for 0.4%. Psychotropic medication, were significantly associated with incident GAD, whereas high low-density lipoprotein (LDL)-cholesterol decreased the risk (Table 2). A marginal positive association was also observed with high waist-to-hip ratio. The same results were found when restricting the analyses to non-demented participants having completed the baseline examination (n=1173, 84.4% (95% CI=7.1–9.7%) of the participants without GAD at baseline developed GAD over 12 years; the incident rate being 10 per 1000 person-years. Multivariate Cox models included baseline covariates meeting Martingale residual criteria for proportionality of risk and associated with incident GAD in Cox models adjusted for age and sex (P<0.15) and were used. The same results were found when restricting the analyses to non-demented participants having completed the baseline examination (n=1173, 84.4% (95% CI=7.1–9.7%) of the participants without GAD at baseline developed GAD over 12 years; the incident rate being 10 per 1000 person-years. Multivariate Cox models included baseline covariates meeting Martingale residual criteria for proportionality of risk and associated with incident GAD in Cox models adjusted for age and sex (P<0.15) and were used. The same results were found when restricting the analyses to non-demented participants having completed the baseline examination (n=1173, 84.4% (95% CI=7.1–9.7%) of the participants without GAD at baseline developed GAD over 12 years; the incident rate being 10 per 1000 person-years. Multivariate Cox models included baseline covariates meeting Martingale residual criteria for proportionality of risk and associated with incident GAD in Cox models adjusted for age and sex (P<0.15) and were used.
the AMSTEL study. 3.9% of the participants without baseline psychopathology developed GAD over 3 years (estimated incident rate was 12 per 1000 person-years) and only a personal history of depression and/or anxiety was significantly associated with incident GAD symptoms, and decline in incapacity for activities of daily living was specific to GAD comorbid with depression.6 In the NESARC study, 1.6% were new cases of GAD over 3 years (estimated incident rate was 5 per 1000 person-years) and the predictors were being female, narcissistic personality, and PTSD, whereas no significant associations were found with major depression or phobia.7 Both of these studies were limited by only one follow-up examination over 3 years with thus a lower number of incident cases and statistical power. None of them examined psychotropic medication, early environment and chronic or metabolic disorders nor did they differentiate recurrent from first-episode GAD.

In our study, major depression, phobia and past GAD were independent risk factors for incident GAD. Depression and female gender were observed to be risk factors for both first-onset and recurrent GAD, whereas phobia was a significant risk factor for first-onset GAD only, however, the low number of recurrent cases precludes drawing definite conclusions. Taking psychotropic medication was associated with recurrent GAD but not with first-onset GAD despite a > 3-fold higher number of cases, which may reflect a low efficacy of medications in preventing GAD relapse. However, the lack of information regarding medication indication and prescription precluded definite conclusions. The number of cases of other anxiety disorders, especially PTSD and panic disorder, was very low in this elderly sample (n = 3; cf. Table 1) and they were thus not examined. Their low prevalence suggests that they are unlikely to be significant risk factors.

A key finding from this study is that first episodes of GAD in late life are more common than previously believed and are related to specific risk factors, including environmental, intrinsic as well as extrinsic factors, notably age-related chronic disorders (respiratory disorders, arrhythmia and heart failure), lipid levels, adiposity and cognitive impairment. Stress has a significant role in the etiology of these disorders, and they are also known in themselves to generate chronic stress. Conversely, dysfunction of the autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis has been reported in GAD.20,21 Reduced lung function, asthma and chronic obstructive pulmonary disease have been associated with prevalent GAD22,23 and clinical studies on pulmonary rehabilitation treatments have been shown to reduce anxiety symptoms.24 There is some evidence of shared neural substrates for HPA and the respiratory control system with bidirectional connections having been reported for dyspnea.25 Heart failure and arrhythmia are also considered as stress-related diseases associated with dysregulation of autonomic nervous system and HPA axes.26,27 A recent case–control study in young adults reported an association between worry, the cardinal symptom of GAD, and a diminished heart rate stress response independent of GAD, with a possible suppression of adrenergic sympathetic stress responses in GAD specifically.28

In response to chronic stress, the de-regulation of the autonomic nervous system and HPA axis could lead to metabolic alterations.29 In our study, lipid levels and adiposity were associated with GAD differently. The fact that higher abdominal obesity but not general body mass was a risk factor for incident GAD is consistent with an over-reactivity of the HPA axis. On the other hand, high LDL-cholesterol but not ischemic or vascular pathologies were associated with decreased GAD incidence, which may be consistent with neural mechanisms. Controversial findings have been found in cross-sectional studies with nonsignificant, positive or negative associations with cholesterol.30 A few small studies showed an inverse association between anxiety and LDL-cholesterol in young adults.31,32 LDL-cholesterol is the major carrier of cholesterol, notably required for the regulation of cell membrane viscosity. Increase in serum LDL-cholesterol could be associated with increased brain cell membrane cholesterol, and changes in density and functioning of neurotransmitter transporters or receptors.33 We have already reported a negative association and interaction with serotonin transporter for late-life depression34 and experimental studies suggested that cholesterol may influence cholecystokinin and GABA receptors.35

Cognitive function was previously examined using Mini-Mental State Examination in two prospective studies, the AMSTEL study on GAD3 and the Longitudinal Aging Study Amsterdam on anxiety symptoms,36,37 showing no significant associations. A few small case–control studies supported an association between GAD and deficits in cognitive control (that is, inhibitory control in interference task, processing speed and shifting of attention in the Trail Making Test, verbal fluency).38 In our study, performance on the Trail Making Test and Mini-Mental State Examination were also associated with incident GAD in the Cox model only adjusted for sex (cf. Table 1) but not in multivariate models. Verbal fluency gave the most significant and robust data, and was the only task specifically associated with cases of GAD occurring after 50 years of age.39 The directionality between anxiety and cognitive control is currently uncertain; our results indicating that pre-existing cognitive deficits, notably tests depending on prefrontal processing, increase the risk of late-onset GAD.

A final noteworthy finding from our study is that in contrast with the AMSTEL study, lifetime stress exposure to adverse events, both recent and distal (more than 50 years before), were independently associated with incident GAD. Lifetime threatening events have been associated with the onset of GAD in young adults.5 Two cross-sectional studies did not find significant associations between prevalent GAD in elderly people and recent or early adverse events, for example, sexual and physical abuse, parental loss and neglect.38,39 In our study, poverty, parental loss or separation and low affective support were significantly associated with incident GAD. Negative parenting behavior and insecure attachment have already been associated with GAD in children and young adults.40,41 Exposure to stressful events has been associated with CNS dysfunction and marked long-term changes in brain circuitry regulating stress reactivity involving the HPA axis.42 We have already reported in this cohort that lifetime GAD was associated with increased secretion of cortisol under stress conditions.21 We also found an association between early adverse events and worse verbal fluency,43 as well as between cortisol levels and verbal fluency.44 Interestingly, in randomized controlled trials, SSRI antidepressants have been reported to improve both GAD symptomatology and also neuropsychological functioning, associated with a decline in cortisol and cognitive improvement.45–47 Whether the HPA axis could act as a mediating factor between stressful events and GAD remains to be examined. In the present study, we also found that a history of mental disorder in parents increased the risk of incident GAD as well reported in younger cohorts.5 This could reflect both early shared environment and genetic vulnerability to anxiety disorder, considering the 30% heritability of GAD and familial link between subtypes of anxiety disorders.48

Limitations to this study should be considered when interpreting the results. Selection bias concerned the recruitment from electoral rolls, the response rate, and the exclusion of institutionalized elderly people, which limits the extent to which these findings can be generalized to the wider community of older adults as study volunteers tend to be younger, better educated and healthier than the overall population. The exclusion of some participants with missing data is also a potential source of bias, these people being older with lower educational level and worse physical and mental health, and thus more likely to be diagnosed with GAD. Although the loss during the 12-year follow-up period was low for an epidemiological study in elderly people and
physical illness well represented in this sample, we could not exclude bias due to loss to follow-up of a more disabled group, which may have led to an underestimation of the actual number of cases and also reduced the overall power of the study. This may also limit the generalizability of our results, and associations may have thus been underestimated. A further limitation was that some of the covariates were self-reported and retrospective (notably for life events especially during childhood) and may have been subject to recall bias with GAD participants responding more negatively about their health. However, similar associations were generally seen in the unadjusted and adjusted analysis, suggesting this is to be unlikely. Participants diagnosed with probable/possible dementia at inclusion were excluded from this analysis to minimize recall bias. However, as such individuals may also have higher rates of anxiety symptoms this could decrease the overall power of the study, possibly underestimating the associations found. Despite extensive adjustments, the possibility remains that unmeasured factors such as other social environment and personality traits may also be involved and confound the associations. Finally, since multiple analyses have been performed we cannot exclude that some associations were due to chance. However, many of the associations reaching traditional significance levels remained significant even after applying overly conservative multiple testing correction.

Conversely, this prospective study is based on a large sample representative of community-dwelling elderly people with five follow-up waves over 12 years, which enhances the accuracy and provides sufficient stability of incidence rate estimates. Extensive information was obtained on clinical status and medication (notably psychotropic medication), which was verified by examining prescription and medications, thus minimizing exposure misclassification. We were able to obtain differential diagnosis of specific anxiety disorders using a standardized psychiatric examination on the basis of DSM-IV criteria with clinical validation of the cases, thus minimizing false positive. Diagnosis was assessed by trained staff (psychologists and psychiatric nurses), which also allowed minimizing false negative. The exact date of GAD event was not always known and the onset was considered to have occurred midway between two assessments to minimize potential recall bias. In contrast with previous studies, we controlled for a large number of potential confounders, particularly lifestyle, early and recent adverse events, measures of physical and mental comorbidities and history of GAD (with a possible risk of over-adjustment), and we could also evaluate predictors of first-onset of DSM-IV mood, anxiety, and substance use disorders in older adults: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2011; 72:144–155.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)
**Baseline characteristics:**

Cohort participants, n=2259

- EXCLUDED: 70 with dementia at baseline

Non demented participants, n=2189

- 215 with missing data on GAD at baseline, 91 with prevalent GAD

Participants free of dementia and GAD at baseline, n=1883

- 172 without follow-up (33 D, 55 no follow-up, 84 follow-up without GAD data)

Participants with at least one follow-up examination, n=1711, 173 events, 143 cases

- 245 with missing data on covariates

Participants included in the longitudinal analysis, n=1466, 154 events, 125 cases

- 293 having not completed the childhood questionnaire

Participants having completed the childhood questionnaire, n=1173, 130 events, 104 cases

**Incidence rate**

**FOLLOW-UP: Participants after**

- **2 years**: 1.70 (0.14)*
  - n=1685, 71 events, 26 W
    - 41 D
    - 17 D
    - 79 D
    - 128 D
  - n=1445, 64 events, 21 W
    - 33 D
    - 90 D
    - 60 D
    - 108 D

- **4 years**: 3.75 (0.17)*
  - n=1604, 56 events, 42 L, 24 W
    - 117 D
    - 79 D
  - n=1374, 51 events, 37 L, 22 W
    - 90 D
    - 60 D
  - n=1013, 16 events, 241 L, 89 W
    - 108 D

- **7 years**: 7.59 (0.22)*
  - n=1174, 21 events, 280 L, 99 W
    - 79 D
  - n=1013, 16 events, 241 L, 89 W
    - 108 D
  - n=935, 16 events, 307 L, 41 W
    - 128 D

- **10 years**: 9.0 (0.30)*
  - n=1077, 17 events, 351 L, 46 W
    - 79 D
  - n=1013, 16 events, 241 L, 89 W
    - 108 D
  - n=803, 13 events, 229 L, 34 W
    - 128 D

- **12 years**: 11.8 (0.43)*
  - n=841, 8 events, 505 L
    - 128 D
  - n=935, 16 events, 307 L, 41 W
    - 128 D
  - n=803, 13 events, 229 L, 34 W
    - 128 D
  - n=738, 7 events, 437 L
    - 128 D

**Fig. S1: Study flow chart**

D: died, L: lost all follow-ups, W: temporary withdrawal from follow-up; * Median (IQR) duration of each follow-up (expressed as years).