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ORIGINAL ARTICLE

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 Neuropsychiatry 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.

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INTRODUCTION

Generalized anxiety disorder (GAD) is a chronic and relatively frequent disorder with lifetime prevalence rates of 5–10%. It commonly precedes major depression and is associated with increased disability, mortality and suicide attempts.[1] Treatment is difficult with a low rate of full remission[2] thus highlighting the urgent need to identify early risk factors for prevention and targeted intervention. GAD is frequently undiagnosed and/or untreated in elderly people notably because of a focus of patients and practitioners on physical symptoms and the general assumption that high rates of anxiety are to be expected in elderly persons due to increased vulnerability.[3] As GAD prevalence peaks in middle age and appears to diminish in elderly people, it is also commonly assumed that older cases principally represent the continuing chronic course of an early-onset illness with very rare new onset in old age.[4] The drop in prevalence may, however, be because of poor case recognition in the elderly due to associated pathologies and differences in clinical presentation; the assumption being that the clinical characteristics of late-onset GAD and its risk factors are the same as for younger persons. Given that GAD is a risk factor for numerous chronic physical and mental disorders with high prevalence in the elderly, the identification of predictors specific to this age group is important for prevention and clinical management, thus having potentially significant consequences for overall health and daily functioning.[3]

Despite its prevalence and impact, knowledge about GAD onset in older people is still scarce, most studies having focused on (young) adults and/or specific populations, and limited or particular risk factors (see Moreno-Peral *et al*.[5] for recent review). Most previous studies have been cross-sectional, which precludes differentiating between factors that co-occur with or result from psychopathology and etiological factors related to the occurrence of GAD. Only two prospective studies have evaluated the 3-year incidence and risk factors for GAD in older adults. Few candidate risk factors (mainly psychopathological) have been identified; history of depression and/or anxiety in the AMSTEL (Amsterdam Study of the Elderly),[6] and being female, posttraumatic stress disorder (PTSD) and narcissistic personality disorder in the NESARC (National Epidemiologic Survey on Alcohol and Related Conditions), the latter being the only study to examine comorbidity with other anxiety disorders.[7] The exposure window to risk factors has thus been very narrow precluding, for example, distal factors such as early or accumulated trauma, longstanding vulnerability with possible biological origins, as well as late-life events, such as age-related chronic and metabolic diseases and adverse life events.

To expand current knowledge of GAD in the elderly, the present study aimed at estimating the 12-year incidence of GAD and describing the predictors of incident GAD in late life in a large cohort of community-living elderly people, using a repeated standardized clinical interview for psychiatric disorder evaluation and a broad range of socio-demographic, lifestyle, biological and clinical risk factors, as well as early and recent adverse events.

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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.[8] 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.[9] 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.[10] 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,[11] 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.[4] 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.[10]

Baseline socio-demographic, lifestyle, biological and clinical variables

The standardized interview included questions on socio-demographic characteristics (age, sex, education level ($\geqslant$5 years)), smoking (current versus ever), alcohol consumption (>12 g per day), diabetes (glycemia $\geqslant 7$ mmol l^{-1} or treated), hypercholesterolemia (cholesterol $\geqslant 6.2$ mmol l^{-1} or treated), hypertension (resting blood pressure $\geqslant 160/95$ 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/m^2) 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 Gospel Oak questionnaire.[12] Mobility limitation, visual and hearing impairment were determined as described.[13] Venous blood samples were taken at baseline after 12-h fasting and lipid levels were measured.[14] Global cognitive function was measured using the Mini-Mental State Examination and a score <26 was considered to be indicative of cognitive impairment.[15] Verbal fluency and visual memory were assessed by reference to Isaacs' Set[16] and the Benton Visual Retention Test,[17] respectively. The Trail Making Tests A and B assessed psychomotor speed and executive function.[18] 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[19] (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[a]

Characteristic	*Total N*	*No GAD*, N = *1568*		*Incident GAD*, N = *143*		P[a]
		N	%	N	%	
Age, years (mean, s.d.)	1711	72.6 (mean)	5.1 (s.d.)	72.4 (mean)	5.0 (s.d.)	—
Socio-demographic characteristics						
Sex (female)	1711	885	56.44	114	79.72	0.0001
Living alone[b]	1708	412	26.33	39	27.27	0.58
Childless	1624	151	10.15	15	11.03	0.95
Education level (⩾5 years)	1710	777	49.59	59	41.26	0.13
Lifestyle						
Alcohol consumption (>12 g per day)	1681	623	40.45	40	28.37	0.46
Smoking (current or ever)	1710	667	42.57	46	32.17	0.95
Physical activity	1513	563	40.62	45	35.43	0.37
BMI (⩾25 kg/m^2)	1701	724	46.41	59	41.84	0.90
WHR (⩾0.94)	1578	313	21.72	22	16.06	0.02
Lifetime adverse events						
Recent adverse events[c]	1667	872	57.11	97	69.29	0.005
Childhood events						
Severe abuse	1365	154	12.33	19	16.38	0.20
Parental loss or separation	1365	412	32.99	52	44.83	0.008
Parents with mental problems	1365	225	18.01	40	34.48	0.0005
Parents had problems with alcohol or drugs	1365	92	7.37	13	11.21	0.17
Conflict, nervous stress at home[b]	1365	195	15.61	29	25.00	0.05
Poverty, financial difficulties	1365	275	22.02	39	33.62	0.001
Parents too often sharing their problems with children	1365	164	13.13	21	18.10	0.17
Parent or adult friend affection	1365	1026	82.15	89	76.72	0.16
Low affective support	1365	174	13.93	28	24.14	0.005
War or natural catastrophe	1365	673	53.88	66	56.90	0.89
Biological and clinical variables						
LDL-cholesterol (>4.01 mmol l^{-1})	1688	500	32.30	38	27.14	0.06
HDL-cholesterol (<1.73 mmol l^{-1})	1698	1042	66.92	80	56.74	0.44
TG (⩾0.95 mmol l^{-1})	1698	1050	67.44	83	58.87	0.27
Hypercholesterolemia (cholesterol ⩾6.2 mmol l^{-1} or treated)[b]	1702	863	55.32	92	64.79	0.34
Hypertension (resting blood pressure ⩾160/95 mm Hg or treated)	1711	695	44.32	64	44.76	0.10
Diabetes (glycemia ⩾7 mmol l^{-1} or treated)	1697	134	8.61	14	9.93	0.12
Ischemic pathologies[d]	1711	220	14.03	13	9.09	0.83
Arrhythmia and heart failure	1705	198	12.67	23	16.20	0.04
Respiratory disorders (dyspnea, asthma, or bronchitis)	1711	73	4.66	14	9.79	0.0007
Osteoporosis	1696	273	17.54	41	29.29	0.18
Thyroid disorder	1700	111	7.13	14	9.79	0.89
At least one chronic disorder[e]	1711	973	62.05	89	62.24	0.21
MMSE (<26)[b]	1703	196	12.56	26	18.31	0.03
Isaacs Set test score (lowest tertile)	1682	394	25.52	42	30.43	0.009
Benton Visual Retention Test score (lowest tertile)	1695	312	20.09	34	23.94	0.05
Trail Making Test A score (highest tertile)	1686	419	27.12	48	34.04	0.003
Trail Making Test B score (highest tertile)	1641	421	27.97	45	33.09	0.02
Visual impairment	1597	88	6.02	11	8.21	0.10
Hearing impairment	1703	64	4.10	4	2.80	0.88
Mobility limitation	1705	59	3.78	8	5.59	0.06
Number of somatic medications ⩾4	1711	698	44.52	75	52.45	0.01
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	NA[f]
Panic disorder	1710	3	0.19	0	0.00	NA[f]
Obsessive compulsive disorder	1711	6	0.38	1	0.70	NA[f]
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. [a]Cox model with delayed entry adjusted for age as time scale and sex (except when sex was examined). [b]Variables not meeting Martingale residual criteria for proportionality of risk. [c]At least one recent adverse event during the past year. [d]Ischemic pathologies correspond to angina pectoris, myocardial infarction, stroke, cardiovascular surgery and arteritis. [e]Chronic disorders correspond to hypercholesterolemia, hypertension, diabetes, asthma, osteoporosis, thyroid disorder and recent cancer. [f]Not applicable (NA) due to the low number of cases.

Table 2. Multivariate Cox Model with delayed entry of incident GAD over 12-year follow-up ($n = 1466$, 125 cases)[a]

Characteristic	*Model 1*			*Model 2*		
	HR	*95% CI*	P	*HR*	*95% CI*	P
Sex (female)	3.38	1.93–5.90	< 0.0001	3.17	1.81–5.55	< 0.0001
Waist-to-hip ratio (WHR ⩾ 0.94)	1.83	0.98–3.44	0.060	1.86	0.99–3.50	0.054
LDL-cholesterol (>4.01 mmol l^{-1})	0.62	0.42–0.94	0.023	0.60	0.40–0.90	0.013
Arrhythmia and heart failure	1.67	1.04–2.70	0.035	1.72	1.07–2.77	0.027
Respiratory disorders (dyspnea, asthma or bronchitis)	2.81	1.57–5.03	0.0005	3.02	1.68–5.41	0.0002
Isaacs Set test score (lowest tertile)	1.49	1.00–2.23	0.048	1.50	1.00–2.23	0.048
Recent adverse events	1.73	1.17–2.55	0.006	1.64	1.11–2.42	0.013
Use of psychotropic medication	1.58	1.00–2.50	0.049	1.64	1.03–2.59	0.036
Current major depression	3.47	1.75–6.90	0.0004	3.55	1.76–7.12	0.0004
Current phobia	2.26	1.43–3.56	0.0005	1.93	1.21–3.06	0.006
Past GAD				4.06	2.63–6.26	< 0.0001

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; HR, hazard ratio; LDL, low-density lipoprotein. [a]Multivariate 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 reduced using a backward selection procedure keeping in the final model all the covariates significant at $P < 0.15$.

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%; anxiolytics for 3.0 and 2.2% took both of them.

Risk factors for incident GAD

The median (interquartile range) duration of the follow-up was 9.7 (7.4) years. Over the 12-year follow-up, 143 of the 1711 participants (8.4%, 95% confidence interval (CI) = 7.1–9.7%) without GAD at baseline reported a new episode of GAD, being the first onset for 80%. The median (interquartile range) age at incident GAD diagnosis was 74.8 (7.9) years and the median (interquartile range) time of diagnosis from baseline examination was 2.6 (2.2) years. The median (interquartile range) age of first onset for recurrent cases was 40 (28) years. The estimated incident rate was 10 per 1000 person-years. Multivariate Cox models with delayed entry were performed with the subjects having no missing data on the covariates included in the complete model 2. In multi-adjusted model 1 using backwards selection removal criteria at $P < 0.15$, being female, having respiratory disorders, arrhythmia and heart failure, lower Isaacs score, current depression, phobia, reporting recent adverse life events and using 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 associations were found after further adjustment for past GAD, which was also highly significantly associated with incident GAD (model 2).

The same results were found when restricting the analyses to subjects with a first episode of GAD (that is, without a history of past GAD, Table 3), except for the use of psychotropic medication ($P = 0.23$). On the other hand, for the participants with recurrent GAD ($n = 28$), only sex (hazard ratio (HR) = 3.55, 95% CI = 1.21–10.41, $P = 0.02$), major depression (HR = 5.82, 95% CI = 1.32–25.71, $P = 0.02$) and psychotropic medication (HR = 2.36, 95% CI = 1.00–5.60, $P = 0.05$) were associated with occurrence of a new episode and no significant associations were found with phobia (HR = 2.19, 95% CI = 0.87–5.54, $P = 0.10$), recent trauma (HR = 1.92, 95% CI = 0.84–4.40, $P = 0.12$) or any chronic disorder ($P > 0.35$).

Table 3. Multivariate Cox Model with delayed entry for first onset of incident GAD ($n = 1367$, 97 cases)[a]

Characteristic	*HR*	*95% CI*	P
Female gender	3.43	1.83–6.41	0.0001
Waist-to-hip ratio (WHR ⩾ 0.94)	1.89	0.93–3.85	0.077
LDL-cholesterol (>4.01 mmol l^{-1})	0.50	0.31–0.82	0.006
Arrhythmia and heart failure	1.91	1.15–3.18	0.013
Respiratory disorders (dyspnea, asthma or bronchitis)	2.95	1.57–5.55	0.0008
Isaacs Set test score (lowest tertile)	1.61	1.03–2.50	0.035
Recent adverse events	1.72	1.11–2.68	0.016
Current major depression	3.60	1.69–7.67	0.0009
Current phobia	2.55	1.51–4.30	0.0005

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; HR, hazard ratio; LDL, low-density lipoprotein. [a]Multivariate models included baseline covariates meeting Martingale residual criteria for proportionality of risk and associated with first onset of incident GAD in Cox models adjusted for age and sex ($P < 0.15$) and were reduced using a backward selection procedure keeping in the final model all the covariates significant at $P < 0.15$. Psychotropic medications initially included were not retained in the final model ($P = 0.23$).

Impact of childhood environment on incident GAD

Of the 1173 non-demented participants having completed the childhood questionnaire and free of prevalent GAD and with no missing variables for covariates, 104 had incident GAD during the 12-year follow-up. In fully adjusted Cox model 1 with backwards selection removal criteria at $P < 0.15$, significant associations were found for parental loss or separation (HR = 1.58, 95% CI = 1.06–2.34, $P = 0.02$), parents with mental problems (HR = 1.75, 95% CI = 1.16–2.63, $P = 0.007$), financial difficulties (HR = 1.65, 95% CI = 1.08–2.52, $P = 0.02$) and low affective support (HR = 1.77, 95% CI = 1.12–2.80, $P = 0.01$) independent of the other factors.

DISCUSSION

In this large prospective study in community-dwelling elderly, 8.4% (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. This was a first episode for 80% of cases. A large range of risk factors of late-life incident GAD were identified; being female, reporting recent and childhood adverse events, having chronic physical and mental health disorders. Most of these factors have not been previously reported in the elderly. In

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 prescriptions 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 GAD[22,23] 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.[27,29] 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.[30] We have already reported a negative association and interaction with serotonin transporter for late-life depression[14] and experimental studies suggested that cholesterol may influence cholecystokinin and GABA receptors.[33]

Cognitive function was previously examined using Mini-Mental State Examination in two prospective studies, the AMSTEL study on GAD[6] and the Longitudinal Aging Study Amsterdam on anxiety symptoms,[34,35] 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).[36] 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.[37] 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[6] and NESARC[7] studies, 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 also 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 comorbidity and history of GAD (with a possible risk of over-adjustment), and we could also evaluate predictors of first late-onset GAD specifically.

To our knowledge, this is the most comprehensive prospective study in the general elderly population to date, providing novel information on the incidence and predictors of late-onset GAD over 12 years. Contrary to what is commonly believed, a significant number of cases occur for the first time in late life with specific age-related predictors thus supporting a vulnerability/stress model for onset. Our study suggests longstanding vulnerability with possible biological origins involving stress systems, such as metabolic disorders (adiposity), chronic diseases (respiratory disorders, arrhythmia and heart failure, cognitive impairment) and environment traumatic factors, including early events. GAD appears as a multifactorial stress-related affective disorder. Some of the risk factors identified in this study can be modified by socio-political intervention (childhood environment) or by health care intervention (physical or mental health problems). The identification of psychopathological, health- and stress-related risk factors could be essential for the early identification and treatment of late-life GAD, which is frequent but often undiagnosed, thus having potential major health and socio-economic consequences by decreasing comorbidity, disability and mortality.

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)

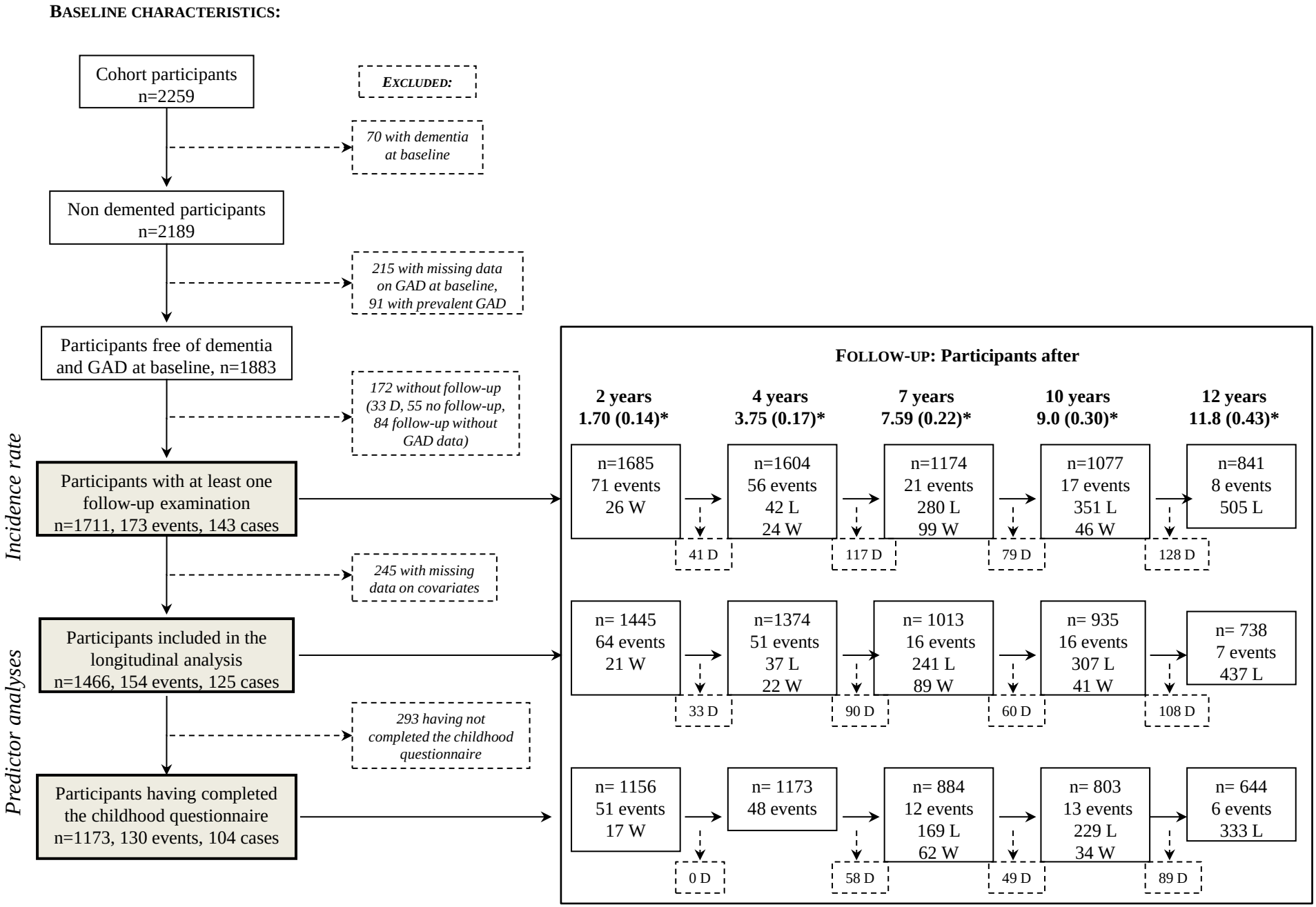

Fig. S1: Study flow chart

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