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Welsh Stroke Alliance

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8 November 2013

STROKE RISK REDUCTION – FOLLOW-UP INQUIRY (supplementary information)

Thank you for the opportunity to submit further written evidence following the recent stroke risk reduction (follow-up) inquiry.

As requested, please find enclosed supplementary written evidence in addition to the evidence previously supplied on behalf of the Welsh Stroke Alliance.

Specifically, we would like to expand on the burden of stroke in Wales, including its economic costs, and the proposals for the development of a National Clinical Network.

It is strongly felt that the development of such a network would be an effective and efficient investment within Wales and go some significant way to satisfy the Health Ministers expectation for the NHS and its partners to *“work with ambition...to make us amongst the best in Europe for stroke treatment and outcomes”*¹.

We do not necessarily think that a link with a cardiac or neurosciences network would service the needs of our stroke patients. However, linking with a proposed vascular (surgery) network could work extremely well.

If you would like more information, please contact Dr Anne Freeman, Chair WSA at anne.freeman2@wales.nhs.uk or on 07889976288.

Yours sincerely



Dr A. Freeman

Chair – Welsh Stroke Alliance

Executive Summary

The physical impact of stroke on the population is well known. It is estimated to consume around 4% of the NHS Wales budget in direct care alone at a cost of around £285 million per year, with the total cost of stroke in Wales, including indirect and social care costs, which are estimated to be three times this amount.

Despite these stark figures, NHS Wales has yet to address the strategic and operational deficiencies that remain.

As you know, services in Wales have seen improvements in the past few years. Both the Welsh Government's tier one acute stroke targets and the Royal College of Physicians (RCP) Sentinel Stroke Audit have reported some significant improvements.

In their most recent (2012) organisational audit report, the Royal College of Physicians go so far as to describe Wales as *"doing well in terms of ensuring that management and clinicians are working together overseeing and running stroke services"*²

However, we feel that more needs to be done to address the generational scale of the stroke problem ahead of us, and there this is best achieved through the effective clinical leadership afforded to us through a resourced clinical network for stroke.

Unlike the other two leading causes of death in Wales (cancer and cardiac), stroke still does not have a dedicated national clinical network. Funded with approximately £300,000 per year, each of the above networks has a dedicated core team driving the development and delivery of these clinical services forward. The Welsh Stroke Alliance calls for parity with these networks. In terms of an "invest-to-save" strategy, the Welsh Stroke Alliance believes this small investment could yield significant savings for NHS Wales (see below).

Regulation of the quality of health care service has risen to the top of the health agenda following the publication of the Francis, Keogh and Berwick reports. The Welsh Stroke Alliance strongly feels that, in light of the significant burden the condition causes to patients and public services, the development of a National Stroke Network would provide a key strategic quality-driven function.

A National Stroke Network would constitute a new organisational model for stroke in Wales, linking professionals and organisations together, traversing traditional organisational boundaries, including the third sector, to achieve improved outcomes for patients and value for money for the NHS.

Through helping translate evidence-into-practice, creating and monitoring service-specific standards for Wales, and working closely with partner organisations in the strategic and operational management of stroke services, the Network would support Welsh Government and NHS Wales in delivering the objectives laid out in *Together for Health: Stroke Delivery Plan*.

Burden of Disease

1) Incidence, Prevalence and Mortality

Of the 30,426 deaths in Wales in 2011, the highest causes of death in Wales remain diseases of the circulatory system (30%), cancer (29%) and diseases of the respiratory system (15%)³⁴

In Wales it is estimated that each year approximately 11,000 people will have a stroke, with an additional 65,100 people living with effects of previous stroke⁵.

2) Economic Burden

A number of studies have estimated the percentage amount of health care expenditure spent on direct stroke care around the world⁶⁷. To date, no such study has taken place for Wales. Below we attempt to estimate possible expenditure based on previous studies.

In one study looking at six developed nations, on average 3% of healthcare expenditure was spent on stroke care, with a minimum of 1.6% being reported for the USA and a maximum of 6.9% reported for NHS Scotland. In a later, separate study NHS England were estimated to spend 4% on direct stroke care.

Based on these rates, it is estimated for the financial year 2011/12 in which Local Health Boards spent a reported £7,127 million, direct stroke care in Wales cost anywhere between £114million to nearly £492million (£114,032,000 to £491,763,000).

If, as is likely, NHS Wales spends the same as NHS England at 4% of its budget on direct stroke care, it cost NHS Wales just over £285million (£285,080,000) for the 2011/12 financial year.

The burden of disease to the population of Wales and its NHS is clear and presents ample opportunity for improvement.

Reducing the Burden

3) Patient Outcomes

In 2006, the Department of Health developed a commissioning tool for stroke services drawing on currently available data, evidence and national statistics to estimate the outcomes and costs of a number of health service strategies to deal with the burden of stroke, including:

<ul style="list-style-type: none">• Prevention with interventions that reduce hypertension• Prevention in patients with atrial fibrillation• Prevention using statins• Prevention through smoking cessation	<ul style="list-style-type: none">• Use of stroke unit on 100 per cent of patients• Use of thrombolysis on 4 per cent or 9 per cent of stroke patients• Use of early supported discharge• One-stop TIA clinics
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The chart below illustrates the estimated impact of these strategies for eight PCTs in central London indicating that hypertension reduction has the greatest potential to reduce the burden of disease, followed by effective AF management, statin prescribing, use of Early Supported Discharge services and 100% use of stroke units. Without a similar study being done in Wales, inference of the impact of these interventions is needed.

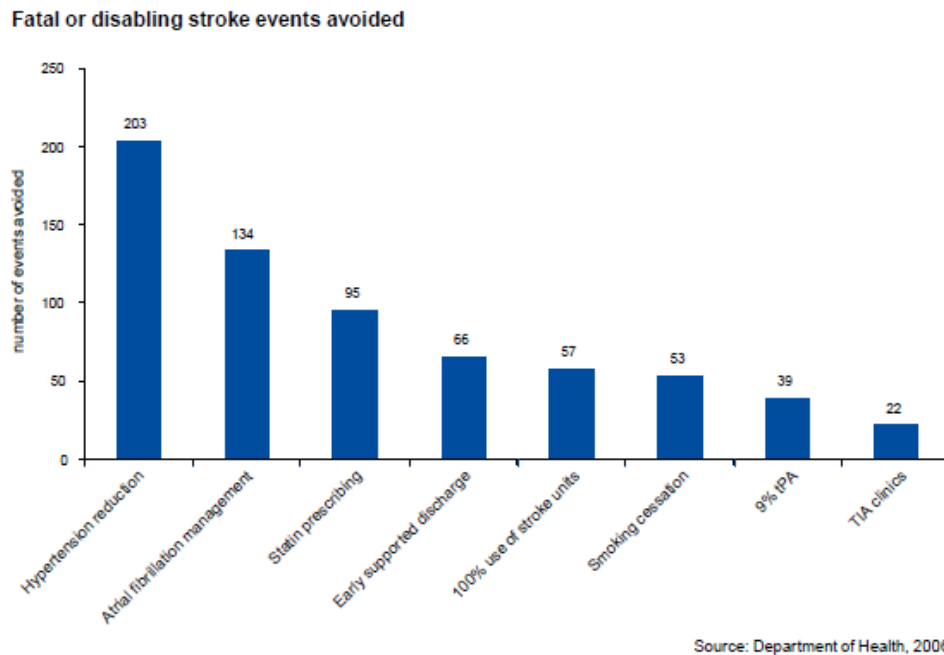


Chart 1: Number of fatal or disabling stroke events avoided

4) Economic Outcomes

In June 2010, the National Institute of Health and Clinical Excellence (NICE) undertook an analysis of the cost implications of implementing the NICE Quality Standards for Stroke.⁸

Without equivalent research being done in Wales, inferences of the potential impact of a number of key interventions is still demonstrably clear, providing a road-map of activity for any national clinical network and significant return-of-investment for NHS Wales.

Appendix 1, overleaf, outlines in more detail the purpose, potential activities, and structure for our proposed National Clinical Network for stroke.

APPENDIX 1

Development of a National Clinical Network for Stroke

- a) The purpose of a National Stroke Network would be to:
 - i) To bring together representatives from all organisations involved in the planning, commissioning and delivery of stroke care across Wales to promote the rapid and continuous improvement in quality stroke services.
 - ii) To scrutinise, challenge, and develop clinical practice in stroke across Wales, and to develop integrated service planning across the public sector.
 - iii) To act as an all-Wales forum to provide expert multi-disciplinary advice and support to NHS Wales, its Local Health Boards, the Welsh Government, Royal Colleges, interested parties and other associated bodies on all aspects of stroke service delivery.
 - iv) To review the clinical aspects of professional and organisational audits related to stroke care, taking account of developments in evidence, knowledge and practice.
 - v) To advise on national clinical standards, best practice and emerging research.
 - vi) Supporting Local Health Boards, WAST, local government and third sector stakeholders to plan, monitor, and deliver quality stroke services in line with government expectations and clinical guidelines.

Activities of a Network

- b) Knowledge-Management / Business Planning Support, ,

Providing a horizon scanning function and knowledge-management resource for Welsh Health Boards, the network will help shape the future direction of services in Wales with its partners. It will also be instrumental in considering emerging national guidance (for example NICE guidelines), regarding the delivery of stroke services, national audits, or related clinical or service research. The network will also be responsible for the development of national guidelines for Wales where deemed appropriate.

- c) Service Development

The network will support the development of local services and monitor progress nationally . The Network will take a lead role in advising the management of contracts (where appropriate) or planning functions. In conjunction with Health Boards and monitor new activity in the development of tertiary services for Wales.

d) Clinical Governance and Service Monitoring

The Network will support clinical governance arrangements with stakeholder organisations by:

- (a) The development or adoption of clinical standards for service delivery
- (b) The effective implementation of care pathways for specific conditions
- (c) The audit of clinical service delivery against clinical standards and/or national targets.
- (d) Benchmarking of clinical performance between providers in line with proven quality improvement methods.
- (e) Access to the clinical knowledge and expertise of other UK stroke programmes
- (f) The facilitation of planning, training, or service review events to support effective service delivery.

Network Structure

- e) The Network Core Team would lead, co-ordinate and facilitate the activities of the Network, and will consist of:
 - i) A National Clinical Lead for Stroke / Chair (p/t)
 - ii) A National Nursing Lead for Stroke (p/t)
 - iii) A National Therapy Lead for Stroke (p/t)
 - iv) A National Primary Care Lead for Stroke (GP p/t)
 - v) A National Stroke Network Manager (f/t)
 - vi) A Network Support Officer (f/t)
 - vii) Other clinicians (e.g. National Vascular lead) may be co-opted to undertake specific pieces of work as appropriate.
- 5) This team will provide the core support to the Network in delivering against its priorities. It will be supplemented by other skills and resources required to deliver the Network agenda through the flexible use of co-opted expertise. This may include analytical skills, audit support, training and education, or external clinical advice.

¹ Together for Health – Stroke Delivery Plan for NHS Wales up to 2016

² Royal College of Physicians. Sentinel Stroke National Audit Programme (2012)

³ Health Statistics Wales 2013: Summary (10 October 2013)

⁴ Chief Medical Officer Report 2012-13: Healthier, Happier, Fairer, Welsh Government (2013): <http://wales.gov.uk/docs/phhs/publications/131009reporten.pdf> [accessed 4 November 2013]

⁵ Stroke Association available at www.stroke.org.uk/news/stroke-facts-and-statistics-your-area [accessed 4 November 2013]

⁶ Evers et al. 2004. International Comparison of stroke cost studies. *Stroke* 35(5):1209-15

⁷ Saka, McGuire, Wolfe 2008. Cost of stroke in the United Kingdom. *Age and Ageing* 38 (1):27-32

⁸ NICE: Quality Standards Programme. NICE cost-impact and commissioning assessment: quality standard for stroke. June 2010

Additional information from the British Medical Association

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Cymru Wales National Office

General Practitioners Committee (Wales)

David Rees AM
Chair of the Health and Social Care Committee,
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**General Practitioners Committee
(Wales)
Pwyllgor Meddygon Teulu
(Cymru)**

28th October 2013

Dear Mr Rees,

Further to my attendance before your committee investigating stroke reduction, I felt that I should clarify the statements that I made as the time constraints did not allow me to, and I felt that my response needed clarification.

The failure to produce a reduction in stroke admission stems from the active public campaign by the NHS to promote stroke awareness, and advice to dial 999.

The FAST campaign (Facial weakness, Arm or leg weakness, Speech altered and Time – phone 999) has been successful in getting stroke victims to hospital quite quickly, but it has also led to transient ischaemic attacks being admitted and investigated as well, along with the non-stroke causes of neurological symptoms such as complex migraine.

So though the overall picture is of increased admissions, our feeling is that there has been a downward trend in actual stroke over the past five years.

Much was stated about the lack of a stroke register, but we do have one – every general practitioner who subscribes to the quality framework in Wales (and I believe that everyone does) keeps a register of new strokes and TIAs and documents that the appropriate action has been undertaken in the practice, or that the appropriate referral has been made. As far as I am aware, Public Health Wales has access to this data. Thus, there is a Welsh Stroke Register.

For a full-blown stroke this entails immediate hospital referral for imaging, and in the event of an embolic stroke, or infarct, caused by a clot (a significant minority of strokes) then thrombolysis should be undertaken within three hours to reduce the area of damaged brain. This mirrors treatment currently undertaken after myocardial infarction and I believe is commonly available across Wales.

There is, as yet, no known treatment for haemorrhagic stroke, other than rehabilitation, so there is no magic wand. Rehabilitation is currently being researched and there is one arm of a trial looking at intensive very early mobilisation of these unfortunate people. Physiotherapy and occupational therapy is the mainstay of treatment, alongside counselling and psychotherapy, as these victims are invariably depressed by the life-changing catastrophe that has happened to them. I am not sure if anyone has touched on this aspect of care.

Thus, management of stroke victims by rehabilitation and reablement is best provided by a multidisciplinary team in a purpose-built environment to facilitate the optimum recovery.

For TIAs, a cause is sought. Careful examination of the patient is undertaken looking for atrial fibrillation, finding a bruit (noisy blood flow in the neck artery due to narrowing), finding a heart murmur or raised blood pressure.

Referral is essential, as even in the absence of a bruit there may be significant arterial narrowing best demonstrated by a carotid ultrasound scan. Significant narrowing should be referred to a vascular surgeon.

In my locality, frank atrial fibrillation (AF) is immediately anti-coagulated in practice and then referred to a cardiologist – as an early diagnosis may respond to cardioversion (an electric shock to the heart). The patient needs to be anti-coagulated for this to be undertaken, so nothing is lost by early implementation of warfarin. An echocardiogram is necessary as valvular pathology (narrowed or leaking heart valves) increases the risk of clot formation.

Intermittent AF may be more dangerous from a stroke point of view as its stop-start nature may precipitate more clots. Diagnosis needs a long-term heart rate measurement – a week or sometimes longer – and this is usually arranged via the cardiologist, who would also have undertaken an echocardiogram. However the patient can help, ask about any changes they have noted in heart rate (such as “palpitations”) and even showing them how to check their own pulse when they have a “turn” may confirm a clinical suspicion. I believe that the threshold for anti-coagulation should be quite low given this clinical picture, and given the catastrophic effects of stroke.

As far as stroke prevention is concerned, then this is definitely in the realm of primary care. I was very surprised at our nursing colleagues whilst extolling the virtues of “nurse consultants” failed to acknowledge the enormous contribution of practice nurses and general practitioners in stroke prevention.

Since starting in practice in 1983, we have always offered “MOTs” for people with health concerns and, though usually only taken up by the worried well, we have picked up quite a variety of pathologies.

This has become refined now and is part of the Quality Framework, with strict blood pressure targets, ECG assessments in practice, cholesterol management and regular medication review.

Prevention is really much better than cure (or the lack of cure) and in conjunction with health improvement legislation such as smoking cessation and alcohol control as already instigated by Welsh Government, then the key to the future is through primary care. Target investment here and the need for specialist intervention will be dramatically reduced.

Despite the popular opinion that we run a coughs and colds service and are always playing golf, British general practice is internationally recognised as in the top three world-class primary care services. It is one of the finest, most cost-effective chronic disease management services in the world. In Wales we have a dedicated work force working beyond capacity.

90% of patient contacts within the NHS occur in primary care, and this is where the biggest changes in health have, and will continue, to occur as long as the resource is provided.

Yours sincerely,

A handwritten signature in black ink, appearing to be 'R. W.', written in a cursive style.

British Medical Association
bma.org.uk

Dr Phil White, GPC (Wales)
British Medical Association

Does Anxiety Affect Risk of Dementia? Findings From the Caerphilly Prospective Study

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Objective: To examine the association of anxiety with incident dementia and cognitive impairment not dementia (CIND). **Methods:** We conducted a prospective study of men aged 48 to 67 years at baseline anxiety assessment; we measured cognition 17 years later. We studied 1481 men who were either eligible for examination or were known to have dementia. Trait Anxiety was assessed using the Spielberger State Trait Anxiety Inventory. Psychological distress was assessed using the 30-item general health questionnaire. Cognitive screening was followed by a clinical examination. Medical notes and death certificates of those not seen were also examined. Outcomes were CIND and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) dementia. **Results:** Of 1160 men who were cognitively screened, 174 cases of CIND and 69 cases of dementia were identified. A further 21 cases of dementia were identified from medical records. After adjustment for age, vascular risk factors and premorbid cognitive function associations with higher anxiety (31st–95th centile) were for CIND odds ratio (OR) 2.31 (95% Confidence Interval (CI) = 1.20–4.44) and for dementia OR 2.37 (95% CI = 0.98–5.71). These associations were slightly stronger for nonvascular (OR = 2.45; 95% CI = 1.28–4.68) than for vascular impairment (OR = 1.94; 95% CI = 0.77–4.89). Analyses of change in cognitive performance, assessed by the Cambridge Cognitive Examination of the Elderly subscales found some evidence for decline in learning memory with higher anxiety score ($b_{\text{age adj}} = -0.291 (-0.551, -0.032)$), but not for any other subscale. **Conclusions:** Anxiety is a risk factor for CIND and dementia. The extent to which the association is independent of depression and whether or not it is causal requires further study. **Key words:** anxiety, dementia, CIND, depression, cognitive decline, vascular dementia.

BMI = body mass index; **CAMCOG** = Cambridge Cognitive Examination of the Elderly; **CaPS** = Caerphilly Prospective Study; **CIND** = cognitive impairment not dementia; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **GHQ30** = 30-item general health questionnaire; **GP** = general practice; **Lowess** = locally weighted least squares; **NINDS-AIREN** = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; **STAI** = Spielberger State Trait Anxiety Inventory.

INTRODUCTION

Little is known of the role of anxiety as a risk factor for dementia. A cross-sectional study has reported lower cognitive performance in older persons with high anxiety (1) and a small prospective study has reported an increased risk of cognitive decline for patients with high anxiety (2). Anxiety has also been implicated in the progression from mild cognitive impairment to Alzheimer's disease (3). Prospective evidence also suggests that the related concept of psychological distress, a mixture of anxiety and depression, is associated with Alzheimer's disease (4,5).

There is accumulating prospective evidence, however, that depression is a risk factor for dementia in both clinical and general population samples (6–8). Although some null find-

ings have been reported (9,10), a recent meta-analysis suggested there is a relative risk of 1.87 (95% Confidence Interval (CI) = 1.09–3.20) of dementia in persons with depression (11). These studies have generally not taken into account the considerable comorbidity between depression and anxiety (12–14) or the precedence given to depression over anxiety in the diagnosis of psychiatric symptoms (15). In the present study, we investigate in a general male population sample the association of anxiety with cognitive impairment not dementia (CIND) and dementia assessed after a follow-up averaging 17 years.

METHODS

Study Population and Survey Methods

The Caerphilly Prospective Study (CaPS) has followed a general population sample of men for cardiovascular and cerebrovascular disease since 1979. At the time of the first follow-up examination (phase 2: 1983–1988), when the men were aged 48 to 67 years, the cohort was enlarged to restore representativeness and a psychosocial assessment, including anxiety measurement, was performed. Cognitive function was assessed at the third (1989–91), fourth (1993–95), and fifth (2002–04) phases. This report involves the 2398 men who were part of the reconstituted cohort at phase 2 of the study, which is considered the baseline for the effects of psychosocial exposures (Figure 1).

Baseline Assessment

Psychological assessment included the 20-item trait scale of the State Trait Anxiety Inventory (STAI) (16) and the 30-item general health questionnaire (GHQ30) (17). Other measures included a detailed medical examination and lifestyle history. Measurements included blood pressure, cholesterol, height, and weight. Smoking habit, alcohol consumption, social class, and marital status were identified by questionnaire. Alcohol consumption was converted to an estimated number of ml per week based on the reported frequency of consumption of different types of drink. After complete description of the study to the subjects, written informed consent was obtained.

Ascertainment of Cognitive Impairment

Cognitive screening at the fifth examination was used to identify men eligible for medical assessment. The criteria were a) all men with Cambridge Cognitive Examination of the Elderly (CAMCOG) score of <83; b) all men

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Received for publication February 21, 2008; revision received November 6, 2008.

This work was funded by the Alzheimer's Society. The Caerphilly Study was funded by the former MRC Epidemiology Unit (South Wales) and was funded by the Medical Research Council of the United Kingdom.

DOI: 10.1097/PSY.0b013e3181a6177c

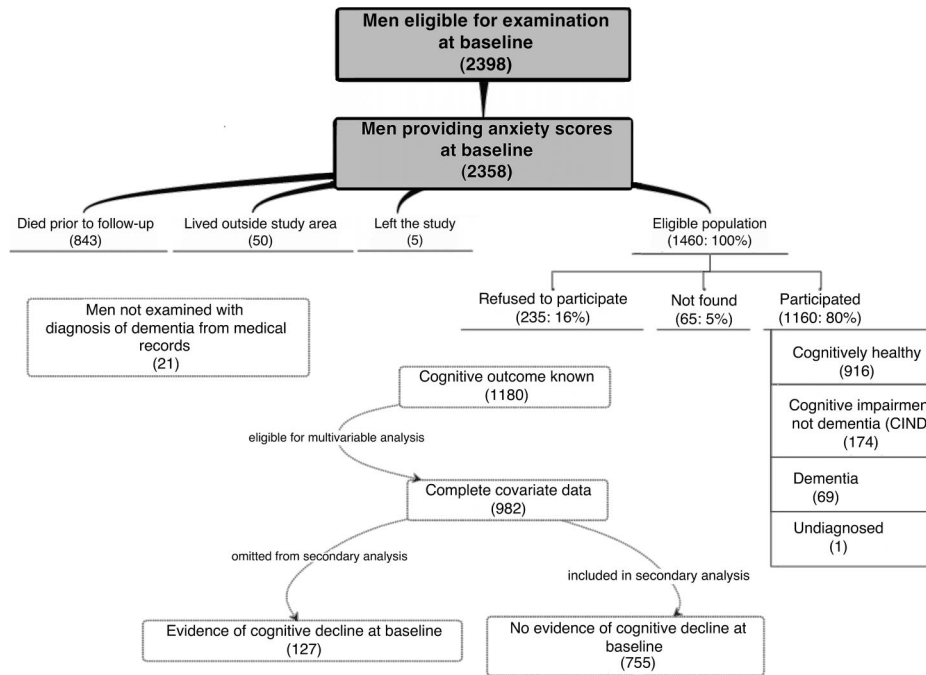


Figure 1. Cohort recruitment.

whose decline in CAMCOG score between any two cognitive assessments was ≥ 10 points; and c) all men who failed to produce a CAMCOG score despite an attempt to do so (18).

The medical assessment included the modified Cambridge Mental Disorders of the Elderly Examination subject and informant interview (19), a neurological examination, the Rosen-modified Hachinski Score, (20), the Frontal Assessment Battery (21), the Clinical Dementia Rating scale (22), and the Informant Questionnaire on Cognitive Decline in the Elderly (23). Where appropriate, all available general practice (GP) records and hospital records were reviewed. All subjects who had died were identified by “flagging” at the National Health Service Central Register. Those with a cause of death recorded as dementia or Alzheimer’s disease were followed up by detailed review of GP and hospital records to confirm diagnosis. The names of subjects who had failed to attend the interview for the initial cognitive assessment were also checked against records of the local Community Mental Health Team for Older People and those known to the service were followed up.

A diagnosis of dementia was made by consensus based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (24). Subjects who were screen positive, but did not exhibit significant impairment in daily functioning sufficient to warrant dementia diagnosis, met the criteria for CIND (25,26); all other screened subjects were classed as cognitively healthy.

Subjects with dementia or CIND were classified as having a likely vascular component if they had clinical features consistent with cerebrovascular disease, operationalized as Rosen revised Hachinski Ischemic Score of ≥ 3 , and for demented subjects if they fulfilled the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria for possible or probable vascular dementia. All other subjects with dementia (including probable Alzheimer’s disease, dementia with Lewy bodies, Parkinson’s disease dementia, fronto-temporal dementia), or CIND (including amnesic mild cognitive impairment) were classified as nonvascular. Details of the diagnostic procedures are given elsewhere (27).

Statistical Methods

Only men whose cognitive status had been determined were included in the analysis. For descriptive purposes, the STAI was dichotomized at the median (Table 1). For analytical purposes, owing to the distribution of the STAI being positively skew, raw STAI scores were \log_e transformed. Pre-

liminary analysis was conducted using locally weighted least squares (Lowess) smoothing plots. These provide model independent plots of the probability of impairment at the fifth examination as a function of the anxiety score and informed the choice of an appropriate model for the relationship. These analyses suggested that the risk of impairment increased markedly above the 30th centile (STAI score = 31) of the anxiety distribution (Figure 2) with little dependence on the anxiety score below that. As a result, piecewise linear logistic regression was used to model the relationship between cognitive impairment and anxiety, allowing for different models in the different ranges of anxiety score; the knot point for the analysis being at the 30th centile. Therefore, odds ratios (ORs) were calculated to identify associations for men at or below the 30th centile and for men at or above the 31st centile. The ORs for men above the knot point were scaled so that they represented the change in risk between the 31st and 95th centiles. This provides a more widely relevant estimate of effect size. Models were checked by analysis of the residuals.

For all multivariable analyses, adjustment was made for age. Adjustment was then made for standard vascular risk factors. Blood pressure, body mass index (BMI), and total cholesterol were modeled as continuous variables. Alcohol consumption (measured in ml/week) was log transformed as $\ln(4 + \text{alcohol})$, the addition of 4 allowing the log transformation of zero for nondrinkers; the resulting variable was modeled as a continuous variable. Social class was modeled as a two-level factor (manual, nonmanual); marital status was modeled as a two-level factor (married or not); and smoking was entered as a three-level factor (never smoked, ex-smoker, current smoker). Evidence of previous vascular disease was a previous heart attack, angina, electrocardiogram ischemia, or intermittent claudication and was modeled as a two-level factor. Although psychological distress, as measured by the GHQ30, assesses both depression and anxiety, it was included in the analysis to provide adjustment for depression at the risk of overadjustment for anxiety. GHQ30 was scored in the usual manner with a score of ≥ 5 denoting psychological distress. National Adult Reading Test score was modeled as a continuous variable to adjust for premorbid cognitive function. Men whose CAMCOG score declined between phases 3 and 4 and between phases 4 and 5 were defined as having evidence of possible impairment at the time of psychosocial assessment (phase 2), i.e., an ongoing process of detectable decline that was detectable early in the study.

The association of anxiety with quantitative change in cognitive performance was analyzed by linear regression of standardized (z) scores for change

ANXIETY AND DEMENTIA

TABLE 1. Baseline Characteristics of 2358 Men With Baseline Anxiety Scores According to Follow-Up Status

Covariates	Men in Follow-Up			All (n = 1160)	Men With Anxiety Scores Not Followed (n = 1195) ^a	p Value for Follow-Up/ Not Follow Up Difference
	Low Anxiety (20 to 34) (n = 575)	High Anxiety (35 to 72) (n = 585)	p Value for Low/High Difference			
Manual social class	334 (58%)	382 (65%)	.01	716 (62%)	863 (72%)	<.0005
Education (no qualifications)	213 (39%)	281 (51%)	<.0005	601 (55%)	334 (43%)	<.0005
Married	528 (92%)	520 (89%)	.09	1048 (90%)	1024 (86%)	<.0005
Current smoker	187 (33%)	228 (39%)	.02	415 (36%)	618 (52%)	<.0005
Prevalent vascular disease	97 (17%)	122 (21%)	.08	219 (19%)	390 (33%)	<.0005
GHQ30 positive (≥5)	36 (7%)	195 (36%)	<.0005	231 (21%)	256 (23%)	.27
Mean age, years (SD)	56.2 (4.3)	56.0 (4.5)	.53	56.1 (4.4)	57.6 (4.5)	<.0005
Mean SBP, mm Hg (SD)	145 (21)	144 (22)	.75	144 (22)	148 (23)	.0001
Mean DBP, mm Hg (SD)	84 (11)	85 (11)	.81	84 (11)	85 (13)	.31
Mean BMI (SD)	26.8 (3.4)	26.5 (3.4)	.13	26.6 (3.4)	26.3 (3.8)	.02
Mean Ln (4+alcohol) (SD)	4.23 (1.44)	4.34 (1.42)	.17	4.28 (1.43)	4.16 (1.51)	.04
Mean total Cholesterol, Mm/l(SD)	5.64 (0.96)	5.66 (1.04)	.71	5.65 (1.0)	5.62 (1.01)	.56
High anxiety scorers				585 (50%)	690 (58%)	<.0005

^a Numbers vary due to missing data.

GHQ30 = 30-item general health questionnaire; SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index.

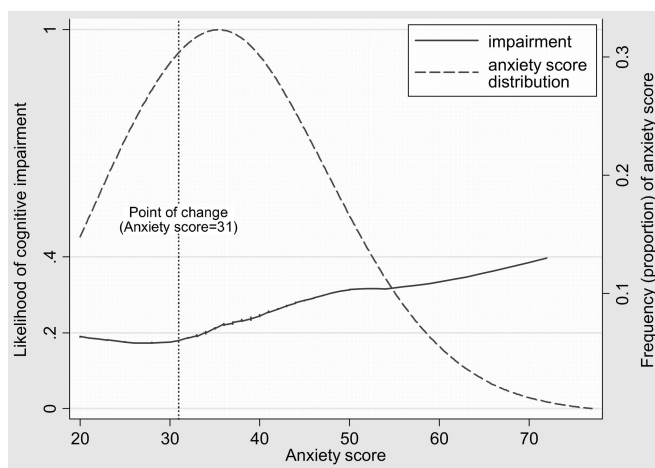


Figure 2. Lowess smoothing of cognitive impairment according to Anxiety score in 1160 men who were cognitively screened.

in CAMCOG subscales between the 3rd and 5th examinations on anxiety (28). Men who were not cognitively screened were omitted.

All analyses were repeated adjusting for apolipoprotein E (APOE) allelic status. This reduced the available sample size by >250 men and these analyses are not shown. For these analyses, allelic status was assessed as a three-level factor comprising homozygous E₄ (high risk), heterozygous E₄ (moderate risk), and non-E₄ (low risk).

RESULTS

Of the 2398 men assessed at phase 2 of the study, 2358 provided anxiety scores (Figure 1). Of these, 843 died before follow-up, 50 lived outside of the study area, and 5 had previously declined further contact with the study, leaving an eligible population of 1460 (100%). Of these, 235 men refused to participate and 65 were not found, resulting in 1160 (80%) participants. Of the 1160 men who were screened, 69 had dementia, 174 had CIND, and 916 were cognitively healthy.

For one man, a diagnosis could not be reached due to insufficient information. A further 21 cases of dementia were identified through medical notes and death certificates, resulting in 1180 men with cognitive outcome data. Of the 1180 men with cognitive outcome data, 982 had complete covariate data. Of these, 71 had dementia and 128 had CIND. Impairment (dementia and CIND) was considered to be vascular in origin in 62 cases and nonvascular in 137 cases. Of the 982 men with complete covariate data, 127 showed evidence of possible cognitive decline from phase 3 of the study and were omitted from secondary multivariable analyses. The maximum follow-up period was 20 years but averaged at 17.3 ± 1.3 (standard deviation) years.

At baseline, men with raised anxiety were more frequently of manual social class, had no educational qualifications, were current smokers, and were GHQ30 positive (Table 1). Men who were not followed were more likely to be manual social class; have educational qualifications; be married; smoke; have previous vascular disease; show high anxiety; be older; have higher systolic pressure, lower BMI, or lower alcohol intake; and did not differ in GHQ score or serum cholesterol.

Risk of cognitive impairment (CIND or dementia) over 17 years was found to increase with anxiety score (Figure 2). Observation suggested that the increase in risk began around the 30th centile of the distribution. Comparison of the log likelihood between a linear model and a piecewise model with the knot point at the 30th centile showed the piecewise model to be preferable ($\chi^2 = 3.86$, $df = 1$, $p = .05$) and this was adopted for the analyses.

Anxiety was found to be associated with cognitive impairment (CIND or dementia) above the 30th centile of the anxiety scale only (Table 2). Associations of low anxiety scores with impairment did not approach statistical significance (not

TABLE 2. Piecewise Logistic Regression of Cognitive Impairment on Trait Anxiety (31st to 95th Centiles)^a in 982 Men With Complete Data and 755 Men Without Evidence of Cognitive Decline at Baseline

Severity of Impairment	Sample Selection	Model: OR, 95% CI, <i>p</i>				
		Adjusted for Age	Adjusted for Age + Vascular Risk ^b	Adjusted for Age + Vascular Risk + GHQ	Adjusted for: Age + Vascular Risk + NART	Full Adjustment
CIND and Dementia	All men	2.87	2.60	2.37	2.19	1.91
		1.68, 4.88	1.50, 4.51	1.26, 4.62	1.24, 3.88	0.99, 3.68
		<.001	.001	.007	.007	.053
CIND only	Excluding men with evidence of decline at baseline	4.02	3.76	2.93	3.36	2.58
		2.05, 7.91	1.84, 7.69	1.29, 6.66	1.61, 7.01	1.11, 5.99
		<.001	<.001	.010	.001	.027
CIND only	All men	2.85	2.62	2.80	2.31	2.32
		1.55, 5.26	1.39, 4.94	1.35, 5.81	1.20, 4.44	1.09, 4.92
		.001	.003	.006	.012	.029
Dementia only	Excluding men with evidence of decline at baseline	3.75	3.60	3.28	3.32	2.98
		1.82, 7.75	1.67, 7.79	1.35, 7.98	1.51, 7.31	1.20, 7.38
		<.001	.001	.009	.003	.018
Dementia only	All men	2.89	2.73	1.91	2.37	1.62
		1.27, 6.54	1.16, 6.45	0.72, 5.09	0.98, 5.71	0.59, 4.41
		.011	.022	.19	.056	.59
Dementia only	Excluding men with evidence of decline at baseline	5.04	4.24	2.06	3.60	1.77
		1.24, 20.45	0.92, 19.60	0.38, 11.28	0.74, 17.47	00.31, 10.24
		.024	.07	.41	.11	.53

^a Odds ratios above the knot point scaled to the 31st–95th centile range. Odds ratios below the knot point not shown.

^b Vascular risk factors: social class, marital status, smoking, alcohol consumption, blood pressure, body mass index, total cholesterol, previous vascular disease. OR = odds ratio; CI = Confidence Interval; GHQ = general health questionnaire; NART = National Adult Reading Test; CIND = cognitive impairment not dementia.

shown). The age-adjusted relative odds of impairment from the 31st to 95th centiles was 2.87 (95% CI = 1.68–4.88, $p < .001$). Further adjustment for vascular risk attenuated the association slightly (OR = 2.60; 95% CI = 1.50–4.51; $p = .001$) as did further adjustment for GHQ30 score (OR = 2.37; 95% CI = 1.26–4.62; $p = .007$). Adjustment for premorbid cognitive function score also attenuated the association slightly (OR = 2.19; 95% CI = 1.24–3.88; $p = .007$). The association for the fully adjusted model was 1.91 (95% CI = 0.99–3.68; $p = .053$). For CIND, a closely similar pattern was found. For CIND, the fully adjusted model, the OR was 2.32 (95% CI = 1.09–4.92; $p = .029$). For dementia, the associations were slightly weaker but were markedly attenuated by adjustment for GHQ30 score (OR = 1.91; 95% CI = 0.72–5.09; $p = .19$). If men with evidence of impairment at baseline are omitted, a closely similar pattern is found, associations with anxiety being slightly stronger (OR_{age adj} = 5.04; 95% CI = 1.24–20.45; $p < .024$) although confidence intervals are wider due to reduced sample size.

These associations were investigated further by comparing men with vascular and nonvascular etiology (Table 3). Slightly stronger associations were found for men with nonvascular etiology. After adjustment for age, the OR for nonvascular impairment was 3.28 (95% CI = 1.79–6.01; $p < .001$) and for vascular impairment, the OR was 2.32 (95% CI = 0.95–5.25; $p = .06$). These associations were slightly stronger after omitting men with evidence of impairment at baseline.

Associations of anxiety with quantitative changes in CAMCOG subscales over time were also investigated (Table 4). This analysis was conducted on 963 men with both phase 3 and phase 5 CAMCOG data available. Anxiety was associated with decline in learning memory (recall and recognition) ($b_{\text{age adj}} = -0.291$; 95% CI = $-0.551, -0.032$; $p = .028$) and praxis ($b_{\text{age adj}} = -0.259$; 95% CI = $-0.521, 0.004$; $p = .053$) although both associations were lost after further adjustment.

All of the above analyses (Tables 2–4) were repeated, adjusting for APOE status (not shown). APOE had no effect on the association of anxiety with dementia.

DISCUSSION

We have shown that trait anxiety is associated with incident CIND and dementia 17 years later in a population-based prospective study. To our knowledge, this is the first study showing an association of anxiety with incident dementia, although other studies have shown associations of anxiety with the related construct of psychological distress (4,5).

Strengths

The CaPS has achieved high levels of participation throughout and the sample used for this analysis reflected a 79% response rate. Diagnosis of dementia and CIND was obtained through examination of the men and examination of medical records using standard criteria. Anxiety was measured at baseline and before the onset of cognitive impairment, using a widely used standard instrument. A wide range of risk

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TABLE 3. Piecewise Logistic Regression of Type of Cognitive Impairment on Trait Anxiety (31st to 95th Centiles)^a in 982 Men With Complete Data and 755 Men Without Evidence of Cognitive Decline at Baseline

Impairment Subgroup	Sample Selection	Model: OR, 95% CI, <i>p</i>				
		Adjusted for Age	Adjusted for Age + Vascular Risk ^b	Adjusted for Age + Vascular Risk + GHQ	Adjusted for: Age + Vascular Risk + NART	Full Adjustment
Nonvascular	All men	3.28	3.00	2.68	2.45	2.02
		1.79, 6.01	1.61, 5.61	1.30, 5.23	1.28, 4.68	0.95, 4.30
		<.001	.001	.008	.002	.07
Vascular	Excluding men with evidence of decline at baseline	4.31	4.13	3.00	3.65	2.61
		2.04, 9.12	1.87, 9.14	1.20, 7.46	1.61, 8.28	1.02, 6.66
		<.001	<.001	.019	.002	.045
Nonvascular	All men	2.23	2.06	2.05	1.94	1.91
		0.95, 5.22	0.83, 5.11	0.74, 5.67	0.77, 4.89	0.68, 5.37
		.06	.12	.17	.16	.41
Vascular	Excluding men with evidence of decline at baseline	3.23	2.92	2.97	2.76	2.79
		0.91, 11.48	0.74, 11.58	0.64, 13.81	0.68, 11.13	0.60, 13.06
		.07	.13	.16	.16	.19

^a Odds ratios above the knot point scaled to the 31st–95th centile range. Odds ratios below the knot point not shown.

^b Vascular risk factors: social class, marital status, smoking, alcohol consumption, blood pressure, body mass index, total cholesterol, previous vascular disease. OR = odds ratio; CI = Confidence Interval; GHQ = general health questionnaire; NART = National Adult Reading Test.

factors and potential confounders, including psychological distress, was used to reduce the likelihood of confounding. Analyses were repeated omitting men with evidence of cognitive impairment at baseline.

Limitations

The study used the GHQ30 to adjust for psychological distress, which has a substantial depressive component at baseline. The GHQ30 has been validated for depression in this cohort with 90% of GHQ30 cases being depression related (29). The CaPS may have been considered sufficiently large at inception; however, the number of men with cognitive impairment was only just sufficient for the analysis and the subgroup analyses were based on small numbers. Although only men were recruited to the study, associations between anxiety and cognitive impairment in men are important. The high response rate at recruitment makes selection bias unlikely. Loss to follow-up is always an issue in cohort studies, but high response rates were achieved at each examination (27). Men who were not screened had higher anxiety levels (Table 1) and are more likely to be cognitively impaired. This bias is likely to have reduced case detection rather than altered patterns of association as it is unlikely that the exposure outcome association was qualitatively different among those who were followed up compared with those who were not. Baseline cognitive function was determined 5 years after anxiety. Although the incidence of dementia between the ages of 48 and 67 years is extremely low, the possibility that a small number of men were cognitively impaired at the time of anxiety assessment cannot be excluded.

Interpretation

Prodromal Effect of Dementia

These findings are complex and may be interpreted in various ways. Although anxiety measurement was made

when participants were aged 48 to 67 years of age and 17 years before case ascertainment, the possibility that anxiety is an early outcome of a dementing process cannot be discounted. However, analyses were repeated omitting men with evidence of impairment at baseline (decline in CAM-COG score). The repeated analysis is a more certain test of incident dementia and showed highly comparable findings with the initial analysis. It also represents a conservative test of the hypothesis as men who were not impaired at baseline but were impaired at the 10-year follow-up would also be omitted. If these data support a prodromal effect of dementia on anxiety, they indicate that the prodromal effect occurs many years before any detectable cognitive effect. For the same reason, it is unlikely, although not impossible, that higher anxiety is due to self-awareness of very early cognitive decline (30). However, association was found only between anxiety and learning memory estimates of cognitive change over time and not for the other ten subscales. It is unlikely that there was any detectable change in cognitive function at baseline.

Prodromal Effect of Depression

As depression is an established risk factor for dementia, it may be that the association of anxiety with CIND and dementia reflects a prodromal effect of depression on anxiety and it is the underlying depression that leads to dementia, although some would argue that anxiety more typically precedes depression (31). Similarly, associations with anxiety may reflect the comorbidity of anxiety with depression (12,13). In our analyses, we adjusted for GHQ30 score, a measure of psychological distress with a large depression component. The extent to which this adjustment reflects an appropriate adjustment for depression or an overadjustment for anxiety is moot. This adjustment had little impact on the association of anxiety with

TABLE 4. Linear Regression of CAMCOG Subscales on Trait Anxiety in 965 Men With Complete Covariate Data

CAMCOG Subscale	Mean (SD)	Model				
		Adjusted for Age	Adjusted for Age + Vascular Risk Factors ^a	Adjusted for Age + Vascular Risk and GHQ	Adjusted for Age + Vascular Risk and NART	Full Adjustment
Orientation	-0.33 (1.41)	-0.075 (-0.342, 0.192)	0.001 (-0.271, 0.269)	0.008 (-0.263, 0.278)	0.058 (-0.213, 0.328)	0.064 (-0.207, 0.336)
Language comprehension	-0.14 (1.16)	0.58 -0.001 (-0.267, 0.266)	0.99 0.013 (-0.257, 0.284)	0.96 0.018 (-0.253, 0.289)	0.68 0.054 (-0.218, 0.326)	0.64 0.058 (-0.215, 0.330)
Language expression	-0.49 (2.32)	1.00 0.040 (-0.230, 0.309)	0.92 0.108 (-0.164, 0.380)	0.90 0.103 (-0.170, 0.376)	0.70 0.161 (-0.112, 0.434)	0.68 0.155 (-0.119, 0.429)
Remote memory	0.09 (1.08)	0.77 -0.021 (-0.283, 0.241)	0.44 -0.016 (-0.282, 0.249)	0.46 -0.018 (-0.284, 0.248)	0.25 -0.014 (-0.281, 0.253)	0.27 -0.016 (-0.284, 0.253)
Recent memory	-0.76 (0.68)	0.88 0.047 (-0.216, 0.310)	0.90 0.107 (-0.160, 0.373)	0.90 0.104 (-0.164, 0.371)	0.92 0.110 (-0.159, 0.379)	0.91 0.108 (-0.162, 0.377)
Learning: Recall and recognition	-0.95 (2.43)	0.73 -0.291 (-0.551, -0.032)	0.43 -0.234 (-0.495, 0.028)	0.45 -0.230 (-0.491, 0.032)	0.42 -0.179 (-0.441, 0.083)	0.43 -0.177 (-0.439, 0.086)
Attention	-0.01 (1.43)	0.028 -0.115 (-0.379, 0.149)	0.08 -0.073 (-0.341, 0.195)	0.09 -0.082 (-0.350, 0.187)	0.18 -0.062 (-0.332, 0.208)	0.19 -0.070 (-0.341, 0.200)
Praxis	-0.43 (1.66)	0.39 -0.259 (-0.521, 0.004)	0.59 -0.220 (-0.485, 0.046)	0.55 -0.213 (-0.480, 0.053)	0.65 -0.177 (-0.444, 0.090)	0.61 -0.172 (-0.440, 0.096)
Calculation	-0.06 (0.50)	0.053 -0.161 (-0.424, 0.102)	0.11 -0.121 (-0.387, 0.146)	0.12 -0.123 (-0.391, 0.144)	0.19 -0.060 (-0.327, 0.207)	0.21 -0.064 (-0.332, 0.204)
Abstract thinking	-0.06 (1.74)	0.23 0.141 (-0.120, 0.401)	0.38 0.132 (-0.133, 0.400)	0.37 0.119 (-0.147, 0.385)	0.66 0.128 (-0.140, 0.395)	0.64 0.116 (-0.152, 0.384)
Perception	-0.36 (1.72)	0.29 -0.066 (-0.327, 0.195)	0.33 0.017 (-0.281, 0.248)	0.38 -0.026 (-0.291, 0.238)	0.35 0.049 (-0.215, 0.313)	0.37 0.038 (-0.226, 0.303)
Total CAMCOG score	-2.73 (9.77)	0.62 -0.771 (-3.411, 1.869)	0.90 -0.139 (-2.802, 2.524)	0.85 -0.169 (-2.840, 2.502)	0.72 0.414 (-2.255, 3.084)	0.78 0.373 (-2.303, 3.049)
		0.57	0.92	0.90	0.76	0.78

^a Vascular risk factors: social class, marital status, smoking, alcohol consumption, blood pressure, body mass index, total cholesterol, previous vascular disease. SD = standard deviation; CAMCOG = Cambridge Cognitive Examination of the Elderly; GHQ = general health questionnaire; NART = National Adult Reading Test.

nonvascular CIND but did attenuate the association with dementia.

Causal Effect of Anxiety on Cognitive Assessment

Of interest is the stronger association of anxiety with CIND than dementia. It may be that high trait anxiety at baseline implies higher anxiety levels at follow-up and these lead to poorer cognitive performance independently of any pathological implications. It may be that men with dementia are less likely to be affected by performance anxiety than men with CIND. However, that stronger associations were found for nonvascular rather than vascular impairment suggests this is not a full explanation. The lack of association between anxiety and quantitative estimate of cognitive change over time also argues against this explanation.

Causal Effect of Anxiety on Cognitive Status?

A case can be made that these data implicate anxiety directly or indirectly in the causal pathway to dementia. A direct pathway would implicate anxiety in the biologic processes underlying dementia, whereas an indirect pathway would implicate anxiety in affecting lifestyle, for example, which then in turn has biologic effects. Alternatively, both anxiety and dementia may share some underlying biological mechanism.

Evidence linking anxiety to dementia is distal from pathology. Although not previously reported for dementia, associations with anxiety have been reported for Parkinson's disease in prospective as well as case control and register studies (32–34). Whether dementia and Parkinson's disease have sim-

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ilar etiologies remains an issue of debate (35). Associations found here relating anxiety to nonvascular impairment and to decline in recall and recognition are consistent with a greater effect on Alzheimer's disease compared with vascular dementia. However, neither of these strands of evidence excludes a common underlying biological process.

Anxiety has also been shown to be associated with cognitive decline after 3 years in elderly patients, although numbers were small (2). These findings were not confirmed in the present study. This may be due to more distant and so less accurate anxiety assessment in our community sample or to greater opportunity for reverse causality in the patient sample.

Against a causal interpretation is the lack of a robust association with cognitive decline as assessed by the CAMCOG and its subscales. Although an association was found with the change in "learning memory" subscale, and this would be consistent with an effect of anxiety on nonvascular dementia in particular, the association was not robust to adjustment. The association with praxis was less convincing and, given the number of hypotheses tested, may have been a chance effect. Nevertheless, this was a conservative test as 17 men with dementia (24% of available cases) were excluded from the analysis due to the unavailability of cognitive decline data.

Also, against a causal interpretation is the absence of a convincing candidate biological mechanism linking anxiety level with cognitive impairment. The suggestion that APOE may be linked to increased anxiety as well risk of dementia (36) was not supported here. However, if an association had been found, this would have more strongly supported the common underlying pathway hypothesis. Other candidate mechanisms involve the hypothalamic-pituitary-adrenal axis and various neuropeptides (37). The idea of a common biologic pathway linking both anxiety and depression to dementia is attractive. Serotonergic pathways have been implicated in both depression and anxiety and both may now be considered risk factors for dementia (38). For anxiety and/or depression to be linked noncausally to dementia is not uninformative. Pharmacologic interventions for anxiety might still have some cognitive benefit depending how far upstream the target mechanism. An identified common underlying pathway would also provide insight into the biologic complexity underlying these conditions and offer new directions for research.

The analysis suggests a nonlinear association over the range of anxiety scores. Although we consider the study underpowered to describe precisely the shape of the nonlinear relationship, it may be inferred that at lower levels of anxiety, as measured by the STAI, there is no change in risk with increasing anxiety. It may be that the STAI scale is not sensitive to the lower range of anxiety score or that larger studies may show that a linear model or a different knot point is more appropriate. Finally, the size of the ORs should not be misinterpreted. They represent a maximal effect of anxiety, i.e., the change in risk over a wide range of higher anxiety scores rather than per unit change in anxiety raw score. Nevertheless, the associations represent a substantial increase in

risk over a range of anxiety scores commonly found in the general population.

CONCLUSION

High trait anxiety, an "exposure" experienced by many and not just a small number of persons with anxiety disorder, has been shown to be associated with CIND and dementia. The extent to which these associations are independent of depression is unknown although adjustment was made for psychological distress as measured by the GHQ30. Given the comorbidity between anxiety and depression, these data suggest that previously reported associations of depression with dementia are complex and that further prospective studies are needed in which both anxiety and depression are assessed at baseline. The population base of these findings suggests that they have broad relevance and that this is an area deserving much closer attention.

This research was funded by the Alzheimer's Society. Baseline data were obtained from the Caerphilly Study Archive, Department of Social Medicine, Bristol University, UK. Dr. John Gallacher as Principal Investigator has full access to all data of the study and takes responsibility for the integrity of the data and accuracy. We would like to thank Truda Bell and her field team for their excellent work in collecting these data along with members of the cohort for their generous cooperation.

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Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Is Sticky Blood Bad for the Brain?: Hemostatic and Inflammatory Systems and Dementia in the Caerphilly Prospective Study

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Arterioscler Thromb Vasc Biol. 2010;30:599-604; originally published online December 3, 2009;

doi: 10.1161/ATVBAHA.109.197368

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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Is Sticky Blood Bad for the Brain?

Hemostatic and Inflammatory Systems and Dementia in the Caerphilly Prospective Study

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Objective—Hemostasis and inflammation have been implicated in dementia. This study investigates the role of specific hemostatic and inflammatory pathways with incident vascular and nonvascular dementia.

Methods and Results—This was a prospective study of a population sample of men aged 65 to 84 years, with baseline assessment of hemostatic and inflammatory factors and cognition measured 17 years later. The sample included 865 men (59 had dementia and 112 had cognitive impairment, not dementia), free of vascular disease at baseline and for whom hemostatic and inflammatory marker data were available and cognitive status was known. A total of 15 hemostatic and 6 inflammatory markers were assessed. Factor analysis was used to identify hemostatic subsystems. The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurologie criteria were used to identify vascular dementia. By using standardized (z) scores for hemostatic and inflammatory markers, and after adjustment for age and risk factors, vascular dementia was associated with fibrinogen (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.02–2.76), factor VIII (HR, 1.79; 95% CI, 1.09–3.00), and plasminogen activator inhibitor 1 (HR, 3.13; 95% CI, 1.73–5.70). For vascular dementia, the HR risk from high levels of all three hemostatic variables (fibrinogen, factor VIII, and plasminogen activator inhibitor 1) was 2.97 ($P < 0.001$). Inflammatory factors were not associated with vascular dementia.

Conclusion—The associations of these hemostatic markers with vascular dementia may implicate clot formation as the primary mechanism and are consistent with a microinfarct model of vascular dementia. (*Arterioscler Thromb Vasc Biol.* 2010;30:599-604.)

Key Words: dementia ■ hemostasis ■ inflammation ■ cognition ■ aging

Hemostasis and the inflammatory response are complex and interrelated processes that are associated with a variety of phenotypes, including cardiovascular diseases.¹ There is limited case-control evidence associating markers of hemostasis and inflammation with dementia.^{2–6} Limited prospective data come from the Rotterdam Study, which found that fibrinogen, but not C-reactive protein (CRP), was associated with incident dementia at the age of 6 years.⁷ Therefore, further studies of hemostatic and inflammatory markers and risk of dementia (both vascular and nonvascular) are required.

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Hemostasis involves a delicate balance of several closely related subsystems or pathways. It is possible, therefore, that associations with these responses reflect the impact of spe-

cific pathways rather than of individual biomarkers. One area of interest is whether hemostatic markers can be analyzed within the context of the coagulation pathways that they represent and whether these pathways can be used to identify more closely the mechanisms associated with cognitive impairment. In the Caerphilly Prospective Study, a wide range of available hemostatic markers allows the comparative influence of several pathways to be assessed.⁸

Methods

The Study Population

Between 1979 and 1983, all men aged 45 to 59 years within the locality of Caerphilly in South Wales, England, were invited to participate. Of the 2818 men found eligible, 2512 (89.1%) were recruited. For the second examination (1985), the original cohort was supplemented with all men of a similar age who had moved into the

Received February 17, 2009; revision accepted November 6, 2009.

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Arterioscler Thromb Vasc Biol is available at <http://atvb.ahajournals.org>

DOI: 10.1161/ATVBAHA.109.197368

area since the first examination. A total of 2398 men were seen and provided blood samples.⁸ Data on hemostatic and inflammatory markers were available for 2318 men. Not all the hemostatic and inflammatory markers were assessed for all men, because of progressive depletion of stored plasma samples.⁹

At the third (1993), fourth (1996), and fifth (2004) examinations, cognition was assessed. At the fifth examination, when the men were aged 65 to 84 years, cognitive assessment was used to identify men eligible for neurological examination to ascertain dementia. Informed consent was obtained from every participant, and the study was approved by the Gwent Research Ethics Committee.

Hemostatic and Inflammatory Markers

A fasting blood sample was obtained during the second examination. In a sample anticoagulated with potassium EDTA, fibrinogen was measured using heat precipitation nephelometry; plasma viscosity, with a Coulter-Harkness capillary viscometer; white blood cell count, in an automated cell counter; and α 2-macroglobulin and α 1-antitrypsin, as previously described.⁸

Activated partial thromboplastin time, activated protein C ratio, fibrinogen, factor VII, and factor VIII (FVIII) were assayed in an MDA-180 coagulometer (Organon Teknika, Cambridge, England).⁸ Fibrin formation time and reaction clotting time were measured by thromboelastography.¹⁰ Activated factor XII, prothrombin fragment 1+2 (Frag I+2), thrombin-antithrombin complexes, tissue plasminogen activator antigen, von Willebrand factor antigen (VWF), and fibrin D-dimer were assayed by enzyme-linked immunosorbent assay^{8,11}; and plasminogen activator inhibitor 1 (PAI-1) was assayed using a chromogenic assay.⁸ High-sensitivity CRP was assayed by immunonephelometry.⁸ Interleukin 6 (IL-6) was assayed using a high-sensitivity enzyme-linked immunosorbent assay.¹¹

Ascertainment of Dementia

Cognitive screening at the fifth examination was used to identify men eligible for a neurological examination.¹² The criteria were as follows: all men whose Cambridge Cognitive Examination score was lower than 83 or whose decline in Cambridge Cognitive Examination score between any two cognitive assessments was greater than 10 points or who were unable to complete the CAMCOG were eligible for a neurological examination. For nearly all men, the neurological examination occurred within two months of cognitive screening.

The criteria for dementia and cognitive impairment not dementia (CIND) are detailed elsewhere.¹² Briefly, the neurological examination included the Cambridge Mental Disorders of the Elderly Examination, a cardiovascular and neurological examination¹³; the Rosen-Modified Hachinski Ischaemic Score (HIS)¹⁴; the Frontal Assessment Battery¹⁵; and the Clinical Dementia Rating.¹⁶ With the subject's consent, someone who knew him or her well (usually the next of kin) was identified and approached to complete an Informant Questionnaire on Cognitive Decline in the Elderly and the modified Cambridge Mental Disorders of the Elderly Examination informant interview.¹⁷ Additional questions were asked when appropriate about symptom onset and progression. All available general practitioner and hospital records were reviewed and summarized, with particular attention given to mention of patients' mental state and relevant investigations. All subjects who had died were identified by "flagging" at the National Health Service Central Register in Southport, and their cause of death was noted. Further information was sought on those with a cause of death recorded as dementia or Alzheimer's disease (AD). Subjects with vascular dementia were required to fulfil National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurologie criteria for possible or probable vascular dementia.¹⁸ Subjects not meeting the full dementia criteria and with an HIS of 3 or higher (including history of cerebrovascular disease or consistent lateralizing neurological signs) were classified as having vascular CIND.¹² Subjects who fulfilled the National Institute of Neurological and Communicative Disorders-Alzheimer's Disease and Related Disorders Association criteria for probable AD¹⁹ and who had no clinical features suggestive of cerebrovascular disease (HIS \leq 2 and absence of vascular disease on available neuroimaging) or other causative

disorder were classified as having AD. Subjects with a presentation or clinical course in keeping with AD and features to suggest cerebrovascular disease (operationalized as an HIS \geq 3 or neuroimaging evidence of infarction) were diagnosed as having mixed dementia.²⁰ Subjects fulfilling the standardized diagnostic criteria for other dementia-like conditions were categorized accordingly. Subjects with CIND were classified by cause only if likely cause was apparent. Because of small numbers, all nonvascular conditions were combined for the purpose of analysis.

Statistical Analysis

Hemostatic and inflammatory markers were log transformed where appropriate, and all markers were standardized (ie, *z* scores were calculated). Associations of individual biomarkers with dementia and CIND were performed by Cox regression (STATA 10 software; Statacorp, Tex). Adjustment was made for age, social class, systolic blood pressure, body mass index, smoking status (never smoked, ex-smoker, or current smoker), total cholesterol level, and alcohol consumption. Men with previous vascular disease, intermittent claudication, or stroke were not included. Analyses were repeated adjusting for premorbid cognitive function using the National Adult Reading Test score obtained at the third examination. The Registrar General's classification of social class is a definition of socioeconomic status widely used in England. Social class was modeled as a 4-level indicator variable composed of these levels: I and II, III nonmanual, III manual, and IV and V. To investigate the possibility of a prodromal effect of dementia, Cox regressions were repeated, not including men with evidence of early cognitive decline. Evidence of early cognitive decline was defined as cognitive scores declining consistently from the first cognitive examination.²¹ This is a strong test of the prodromal hypothesis; however, it excludes men whose decline began soon after baseline (second) examination and men whose decline is not the result of a dementing process.

To test the hypothesis that associations with individual biomarkers reflect the operation of specific coagulation pathways on vascular dementia, structural equation modeling (SEM) was used. SEM allows variables to act dependently and independently and enables the putative causal pathway to be modelled. A two-step procedure was used. First, specific coagulation pathways were identified by exploratory factor analysis. Structural modelling (using EQS software) was then used to estimate the association between the latent variables representing specific coagulation pathways and dementia. The fit statistics used to evaluate the fit of the data to the hypothesized coagulation pathways and dementia were the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). The SEM glossary describes the coefficients that are shown (Figure). These are as follow: (1) standardized path coefficients (single-headed arrows) that are standardized regression coefficients and indicate the association between dependent and independent variables, (2) standardized residual covariances (double-headed arrows) indicating associations between independent variables not accounted for in the model, and (3) standardized residual variances (adjacent to independent variables) indicating measurement error for the observed independent variables. An introduction to SEM is provided as electronically available supplementary material (available online at <http://atvb.ahajournals.org>).

Results

Of the 2318 men with data on hemostatic and inflammatory markers, 750 were known to have died before the current phase of the study, leaving 1568 considered to be alive; 1429 of these men were eligible for follow-up, with 1137 (79.6%) successfully followed up and cognitively screened. Of these men, 71 were diagnosed as having dementia, 171 were diagnosed as having CIND, and 895 were cognitively healthy. A further 21 men were diagnosed as having dementia from medical records, resulting in the cognitive status being available for 1158 men. Of these men,

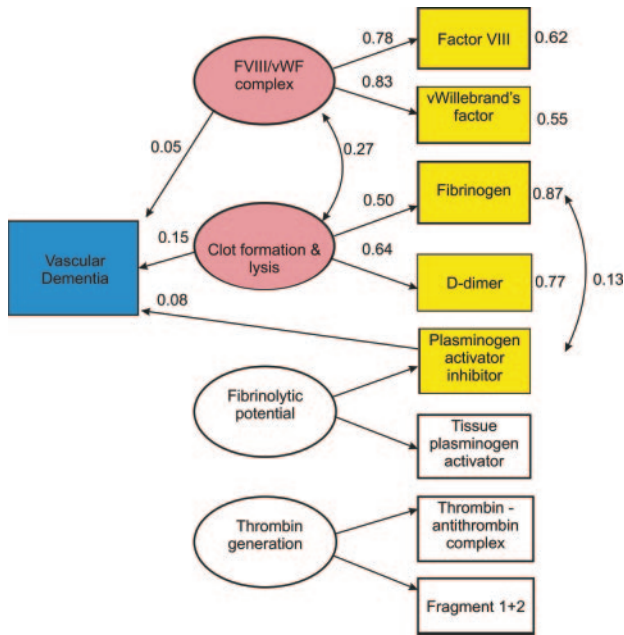


Figure. Structural equation modeling analysis of hemostatic pathways.

865 were free of vascular disease at baseline and available for analysis, of whom 112 had cognitive impairment and 59 had dementia. If men with evidence of early decline are omitted, 744 were available for analysis, of whom 85 were cognitively impaired and a further 42 had dementia. The maximum follow-up was 20 years; however, it averaged 17.3 years (SD, 1.3 years). For the exploratory factor analysis, 476 men had complete data for all hemostatic variables. For structural modeling, 602 men had complete data.

The baseline characteristics of the 1568 men who were alive at the beginning of the study show that men who were not followed up were more likely to be of manual social class (34.8% vs 62.0%; $P < 0.01$) and more likely to be current smokers (44.5% vs 35.9%; $P < 0.01$) and to have a lower cognitive function (National Adult Reading Test mean, 21 vs 25; $P < 0.01$). They did not differ significantly in age or body mass index, and any differences in blood pressure were small. Regarding hemostatic markers, all differences were slight, with men who were not followed up having a longer activated partial thromboplastin time (mean, 33.4 vs 32.9 seconds; $P = 0.04$) and higher levels of D-dimer (mean, 82.2 vs 78.0 ng/mL; $P = 0.05$), factor XIIa (mean, 3.23 vs 3.02 ng/mL; $P = 0.04$), and tissue plasminogen activator antigen (mean, 11.9 vs 11.2 ng/mL; $P < 0.01$). Men who were not followed up also had slightly higher levels of the inflammatory markers $\alpha 2$ -macroglobulin (mean, 15.7 g/100 g vs 15.2 g/100g; $P = 0.03$) and $\alpha 1$ -antitrypsin (mean, 16.7 g/100 g vs 16.1 g/100 g; $P < 0.01$) and substantially higher levels of IL-6 (mean, 4.91 vs 2.20 pg/mL; $P < 0.01$). The following markers required log transformation for the analysis: D-dimer, Frag1+2, thrombin-antithrombin complex, VWF, plasma viscosity, CRP, IL-6, and $\alpha 2$ -macroglobulin.

Associations with cognitive impairment (CIND and dementia) were investigated in 865 men free of vascular disease at baseline (Table 1). After adjustment for age, social class,

systolic blood pressure, body mass index, smoking status, total cholesterol level, and alcohol consumption, an association with vascular impairment was found for fibrinogen. Evidence of association was also found for PAI-1. There was no evidence of association with any of the inflammatory markers. For nonvascular impairment, there was no evidence of increased risk with any of the hemostatic markers or inflammatory markers, although factor VII appeared to have a protective effect.

The analysis was repeated for dementia. For the hemostatic markers, vascular dementia was associated with fibrinogen, FVIII, and PAI-1. The analysis was repeated, excluding men with evidence of early cognitive decline. The smaller numbers reduced the power of the analysis, but the point estimates were closely comparable to those found in the sample as a whole, with the strongest associations being found for fibrinogen (hazard ratio [HR], 1.79; 95% confidence interval [CI], 0.98–3.28; $P = 0.06$), FVIII (HR, 1.77; 95% CI, 0.88–3.57; $P = 0.11$), and PAI-1 (HR, 2.68; 95% CI, 1.22–5.88; $P = 0.04$). For nonvascular dementia, evidence of a protective association was found for the hemostatic marker Frag1+2 and for the inflammatory marker plasma viscosity.

The associations of FVIII, fibrinogen, and PAI-1 with vascular dementia may either reflect a general effect of the coagulation cascade or identify specific coagulation pathways that confer increased risk. These alternatives were investigated by including FVIII, fibrinogen, and PAI-1 in the same analysis to show whether their effects were independent of one another. The presence of a general hemostatic effect would be indicated by the absence of independent associations. The analysis was consistent with each biomarker making some independent contribution to the association: fibrinogen, HR, 2.11 (95% CI, 0.88–5.04; $P = 0.09$); FVIII, HR, 2.09 (95% CI, 1.02–4.31; $P = 0.04$); and PAI-1, HR, 4.39 (95% CI, 1.97–9.77; $P < 0.001$). The combined independent effects of these biomarkers on risk for vascular dementia was 2.97 (95% CI, 1.38–4.56; $P < 0.001$).

The SEM was used to further investigate the relative contribution to risk of vascular dementia of the coagulation pathways represented by the available hemostatic markers. Exploratory factor analysis found four statistical factors corresponding to components of the coagulation pathway (Table 2). The high loadings on statistical factor 1 of FVIII (0.88) and VWF (0.82) were interpreted to represent the FVIII/VWF complex (indicating potential for platelet and fibrin plug formation). High loadings on statistical factor 2 of PAI-1 (0.80) and tissue plasminogen activator antigen (0.75) were interpreted to represent the potential for impaired fibrinolytic activity. High loadings on statistical factor 3 of fibrinogen (0.81) and D-dimer (0.69) were interpreted to represent clotting activity. High loadings on statistical factor four of thrombin-antithrombin complexes (−0.75) and Frag1+2 (−0.77) were interpreted to represent thrombin generation. These statistical factors were used as latent variables for the purposes of structural modeling.

The four-factor structural model (Figure), using the two highest loading biomarkers per latent variable as identified in the exploratory factor analysis (Table 2, boldface), provided a poor fit to the data ($N = 524$, $\chi^2_{22} = 83.46$, $P < 0.001$,

Table 1. Associations of Individual Hemostatic and Inflammatory Markers With Cognitive Impairment and Dementia in 865 Men Free of Vascular Disease and Not Taking Anticoagulants at Baseline*

Type of Marker	Vascular Impairment (n=53)		Non Vascular Impairment (n=133)		Vascular Dementia (n=27)		Non Vascular Dementia (n=26)	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Hemostatic								
Fibrinogen	1.41 (1.01–1.98)	0.04	1.06 (0.80–1.26)	≥0.99	1.68 (1.02–2.76)	0.04	0.77 (0.47–1.28)	0.30
Factor VII	1.05 (0.74–1.50)	0.80	0.74 (0.55–1.00)	0.046	0.98 (0.61–1.55)	0.90	0.86 (0.50–1.47)	0.60
Factor VIII	1.35 (0.92–1.98)	0.10	0.88 (0.67–1.14)	0.30	1.79 (1.09–3.00)	0.02	0.96 (0.62–1.48)	0.90
von Willebrand factor antigen	1.16 (0.82–1.65)	0.40	0.93 (0.75–1.17)	0.50	1.26 (0.77–2.05)	0.40	1.03 (0.66–1.60)	0.90
von Willebrand factor activity	1.12 (0.79–1.60)	0.50	0.99 (0.80–1.23)	0.90	1.32 (0.79–2.20)	0.30	0.99 (0.66–1.47)	≥0.99
Factor XIIa	1.11 (0.74–1.66)	0.60	0.87 (0.64–1.18)	0.40	0.96 (0.53–1.73)	0.90	0.90 (0.52–1.57)	0.70
Activated partial thromboplastin time	1.14 (0.87–1.49)	0.30	1.04 (0.83–1.31)	0.70	1.12 (0.87–1.45)	0.40	1.23 (0.89–1.71)	0.20
Activated protein C ratio	0.89 (0.61–1.31)	0.60	1.18 (0.86–1.62)	0.30	0.97 (0.55–1.68)	0.90	1.31 (0.72–2.37)	0.40
Reaction clotting time	1.07 (0.76–1.50)	0.70	0.92 (0.73–1.15)	0.40	1.08 (0.81–1.44)	0.60	0.98 (0.65–1.49)	0.90
Fibrin clotting time	1.10 (0.82–1.49)	0.50	1.05 (0.84–1.31)	0.70	0.90 (0.48–1.68)	0.70	1.04 (0.69–1.56)	0.90
Fragment 1+2	0.89 (0.56–1.41)	0.60	0.88 (0.63–1.23)	0.40	0.71 (0.41–1.24)	0.20	0.51 (0.26–0.98)	0.04
Thrombin-antithrombin complex	0.87 (0.51–1.48)	0.60	1.12 (0.83–1.50)	0.50	0.75 (0.38–1.50)	0.40	0.79 (0.45–1.39)	0.40
Tissue plasminogen activator	1.00 (0.68–1.46)	≥0.99	0.90 (0.71–1.14)	0.40	1.45 (0.84–2.51)	0.20	0.95 (0.58–1.55)	0.80
Plasminogen activator inhibitor	1.77 (1.13–2.77)	0.01	1.18 (0.88–1.60)	0.30	3.13 (1.73–5.70)	<0.001	1.43 (0.77–2.66)	0.30
D-dimer	0.99 (0.72–1.33)	0.90	1.10 (0.87–1.39)	0.40	1.09 (0.74–1.62)	0.70	1.18 (0.76–1.87)	0.50
Acute-phase inflammatory response								
Plasma viscosity	1.18 (0.80–1.76)	0.40	0.95 (0.75–1.21)	0.70	1.42 (0.82–2.47)	0.07	0.55 (0.31–0.96)	0.03
α2-Macroglobulin	0.86 (0.58–1.29)	0.50	1.08 (0.85–1.37)	0.60	0.68 (0.36–1.29)	0.20	0.99 (0.57–1.73)	≥0.99
α1-Antitrypsin	1.04 (0.71–1.52)	0.80	0.91 (0.71–1.17)	0.50	1.14 (0.65–2.00)	0.60	1.33 (0.82–2.17)	0.30
White blood cell count	0.95 (0.63–1.44)	0.80	0.92 (0.71–1.19)	0.50	1.40 (0.80–2.42)	0.20	0.70 (0.42–1.19)	0.20
C-reactive protein	1.04 (0.66–1.64)	0.90	0.97 (0.74–1.28)	0.90	1.29 (0.69–2.40)	0.40	0.78 (0.42–1.44)	0.40
Interleukin 6	0.90 (0.54–1.49)	0.70	0.87 (0.63–1.21)	0.40	1.05 (0.54–2.04)	0.90	0.66 (0.32–1.35)	0.30

CI indicates confidence interval; HR, hazard ratio.

*Data adjusted for age, social class, systolic pressure, body mass index, smoking, total cholesterol, and alcohol consumption.

CFI=0.90, RMSEA=0.07, SRMR=0.06) and simpler models were sought. The best-fitting model used five observed variables (yellow background) and included two latent variables (pink background) ($N=602$, $\chi^2_6=5.27$, $P=0.51$, CFI=1.00, RMSEA=0.01, SRMR=0.015), explaining 3.5% of the variance in vascular dementia (Figure). The analysis indicated that the latent variables FVIII/VWF complex ($\beta=.05$, $P<0.05$) and clot formation and lysis ($\beta=.15$, $P<0.05$) were associated with vascular dementia. The observed variable PAI-1 was also independently associated with vascular dementia ($\beta=.08$, $P<0.05$). If this analysis is repeated using just the five observed variables with no latent variables, the model fit is poor ($N=602$, $\chi^2_{10}=426.59$, $P<0.001$, CFI=0.03, RMSEA=0.26, SRMR=0.17).

Discussion

In this 17-year prospective study, hemostatic rather than inflammatory markers have been shown to predict vascular cognitive impairment and vascular dementia. Specifically,

fibrinogen, FVIII, and PAI-1, representing the coagulation pathways of clotting activity, platelet and fibrin plug formation, and fibrinolytic potential, were identified as increasing the risk of vascular dementia.

Strengths and Limitations

High levels of participation have been achieved throughout the study, although the sample was composed of men only. The sample used herein reflects an 80% response rate. Diagnosis of cognitive status was obtained through examination of participants and medical records using standard criteria. Hemostatic factors were assayed using standard techniques, and internal laboratory quality assurance was evaluated.^{8,11} Adjustment for a wide range of potential confounding variables was made. Cognitive status was not available at baseline, but adjustment was made for premorbid cognitive function assessed within 5 years of baseline. Men who were not followed up were more likely to have higher levels of some biomarkers and were more likely to be manual social class, to be current smokers, and to have lower cognitive function. These

Table 2. Varimax-Rotated Factors From 476 Men With Complete Hemostatic Marker Data

Hemostatic Marker	Latent Variable			
	1 (Platelet Plug Formation)	2	3	4
Fibrinogen	0.05	0.13	0.81	0.05
Factor VII	0.01	0.58	0.09	0.13
Factor VIII	0.88	0.05	0.09	-0.01
von Willebrand factor antigen	0.82	-0.05	0.18	0.07
Factor XIIa	0.06	0.36	-0.17	-0.48
Activated partial thromboplastin time	-0.69	-0.06	0.27	0.14
Activated protein C ratio	-0.41	-0.20	-0.06	0.22
Reaction clotting time	-0.13	-0.13	0.35	0.01
Fibrin clotting time	-0.01	0.06	-0.25	-0.04
Fragment 1+2	-0.01	0.04	0.11	-0.77
Thrombin-antithrombin complex	0.02	-0.13	0.03	-0.75
Tissue plasminogen activator	0.12	0.75	0.09	0.04
Plasminogen activator inhibitor	-0.05	0.80	0.02	0.05
D-dimer	0.17	-0.01	0.69	-0.28

biases indicate that the current analysis is likely to be conservative. The use of SEM to explore the effect of specific hemostatic pathways is limited to the variables available to the study and does not represent the influence of the coagulation cascade as a whole. Although SEM generated a biologically plausible analysis, the analysis requires confirmation elsewhere. Although sufficiently powered for its intended purpose, the study is small for the present purpose. Despite this, consistent and robust associations were found. However, much larger studies are required for precise estimates of risk to be available.

Interpretation

These analyses address two basic mechanisms that may be related to risk of dementia: inflammation and coagulation. The hypothesis that inflammatory processes increase risk of nonvascular dementia^{22, 23} was not supported. This lack of association may be the result of lack of power or the nonvascular dementia category, including men with mixed dementia and men with AD. Alternatively, it may be that previously reported associations of cognitive decline with inflammatory markers indicate the effects of incipient dementia.²⁴ An apparently protective effect of plasma viscosity for nonvascular dementia is anomalous and likely to be a chance effect.

The hypothesis that hemostasis affects vascular dementia was strongly supported. Our findings confirm those of several case-control studies showing that hemostatic markers are related to vascular dementia in particular,^{4,6} and dementia in general.² Our findings extend this evidence to show prospectively over 17 years that hemostatic markers are associated

with vascular dementia but not nonvascular dementia. Previous prospective evidence has shown that fibrinogen, but not CRP, was associated with vascular dementia.⁷ Our findings extend this evidence to FVIII, PAI-1, and the inflammatory marker plasma viscosity.

Of particular interest are the mechanisms by which hemostatic factors affect risk of vascular dementia. SEM indicated that coagulation pathways (represented by latent variables) provided a better model fit than individual biomarkers. Two coagulation pathways conferred increased risk of vascular dementia. The association with the latent variable "FVIII/VWF complex" implicates the formation of the platelet and fibrin plug, whereas the association with the latent variable "clot formation and lysis" implicates the formation and lysis of the fibrin plug. The association of PAI-1 suggests an additional risk due to impaired fibrinolytic activity. The relative strengths of these associations suggest that clot formation and lysis have the major role. The presence of error covariance linking FVIII/VWF complex and clot formation and lysis (0.27) is consistent with the association of primary with secondary hemostasis. In contrast to the findings in the Rotterdam Study, no independent association was found of vascular dementia with D-dimer, although D-dimer did contribute to the structural model. The association of impaired fibrinolytic potential with vascular dementia implicates fibrinolysis. Whether this is the result of inhibition of fibrinolysis by PAI-1 or is a response to higher coagulation levels is unknown.

Our findings may be attributed to residual confounding. However, the fact that robust associations are found with some hemostatic markers and not others, and with vascular and not nonvascular dementia, argues against this conclusion. Associations with the hemostatic markers are unlikely to reflect reverse causality because attenuation by adjustment for premonitory cognitive function was generally slight and in some cases the association was strengthened. However, all three hemostatic markers associated with vascular dementia are also acute-phase protein reactants.^{1,25} Therefore, it is possible that the associations of fibrinogen, FVIII, and PAI-1 with vascular dementia simply reflect associations with other inflammatory markers rather than associations with hemostasis or fibrinolysis. However, the fact that no association was found with CRP and IL-6 implicates hemostatic rather than inflammatory activity. The analyses excluding men with evidence of early decline demonstrate that a prodromal effect of vascular dementia on hemostatic factors is unlikely to account for the associations found.

These data present a picture of vascular dementia being related to clot formation as the primary mechanism. These data are consistent with a microinfarction model of vascular dementia. The small amount of longitudinal data on cognitive decline supports this conclusion, with some evidence that D-dimer and fibrinogen are associated with decline in global function²⁶ and fluid intelligence.²⁷ The clinical implication of these findings is that reducing clot formation through anticoagulation is likely to result in greater cognitive benefit than just the established benefit of a reduction in ischemic stroke, as suggested in a study of patients with atrial fibrillation.²⁸ However, many of the hemostatic factors identified are

acute-phase reactant proteins; similar associations were observed for plasma viscosity and white blood cell count. Therefore, these associations may also reflect an association of systemic inflammation with vascular dementia.

In conclusion, specific hemostatic mechanisms, notably those related to clot formation and lysis, are related to increased risk of vascular dementia. Further studies are required, however, to confirm these findings and to establish whether there is any cognitive benefit from interventions targeting the clotting process.

Acknowledgements

The Caerphilly Study was undertaken by the former MRC Epidemiology Unit (South Wales) and was funded by the Medical Research Council of the United Kingdom. The database is currently maintained by the Department of Social Medicine, University of Bristol, Bristol, England. We thank Truda Bell, MSc, and her field team for their excellent work in collecting these data and the men of the Caerphilly cohort for their strong support.

Source of Funding

This study was supported by the Alzheimer's Society.

Disclosures

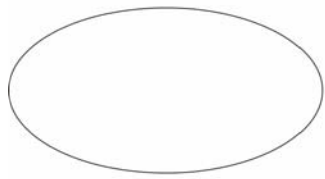
None.

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Observed variables (haemostatic markers and dementia)



Latent variables (haemostatic pathways: from factor analysis)

0.50



Standardised path (regression) coefficient from independent to dependent variable

0.27



Standardised covariance between independent variables: double headed arrow

0.50

Standardised residual (error) variance for independent observed variables (adjacent to the observed variable)

Caerphilly Prospective Study (CAPS)

Introduction

The Caerphilly Prospective Study (CAPS) was set up by the MRC Epidemiology Unit (South Wales). At that time it was the fifth prospective study of cardiovascular disease in the United Kingdom, although only the second population based study, after the British Regional Heart Study.

Its initial aims were to examine the importance of lipids, haemostatic factors, and hormones such as testosterone, cortisol and insulin (Lichtenstein *et al* 1987) in the development of ischaemic heart disease (IHD). Subsequently, other hypotheses were included with a specific interest in platelet function, and psychosocial variables.

With the ageing of the cohort, additional outcomes have been included in particular stroke, hearing problems and cognitive function.

Phase I

The initial design attempted to contact all men aged 45 to 59 years from the town of Caerphilly and adjoining villages. 2512 subjects (response rate 89%) identified from the electoral register and general practice lists were examined between July 1979 until September 1983 (phase I).

Men were initially seen at an evening clinic, where they completed a questionnaire, had anthropometric measures and an ECG taken. They also completed a food frequency questionnaire at home (Fehily *et al* 1994). They subsequently re-attended an early morning clinic to have fasting blood samples for a wide variety of tests.

Quality control was examined by the use of both "blind" split samples as well as a second repeat measure on a random sub-sample to examine intra-individual variation.

Phase II

Phase II was undertaken between July 1984 to June 1988. An additional 447 new men were included who had moved into the study areas. In addition to the tests undertaken at phase I, new tests included audiometry.

Phase III

Phase III was undertaken between November 1989 to September 1993. It followed the same methods as before. The main new features were a standardised battery of cognitive function tests as well as a variety of new platelet and bleeding time tests.

Phase IV

Phase IV, the last time the men were examined, was undertaken between October 1993 to February 1997. Audiometry measured at phase II was repeated as was cognitive function measured at phase III.

All men have been followed up for incident IHD through mortality flagging, self-reported information confirmed by medical records, positive history to the Rose angina questionnaire, checking hospital admissions and new evidence of ECG ischaemia. The WHO criteria were used to define cases of non-fatal myocardial infarction.

At each phase, 40-50 mls of blood were taken and stored at either -40 or -80 C. This insightful decision has enabled subsequent researchers to rapidly test new hypotheses (e.g. the role of H. Pylori, cytomegalovirus and C. Pneumoniae with respect to IHD risk: see Strachan *et al* 1999, 1999, 1998).

A large amount and variety of samples (serum, plasma, sodium citrate, etc.) remain for future potential analyses. Unfortunately, no whole blood was stored from phase I.

Follow-up research

Since that time the men have been contacted on two further occasions by post. This has enabled data on stroke events as well as new non-fatal myocardial infarctions to be collected.

Clinical records of all strokes have been studied in detail and CT scans obtained where possible. In the most recent follow-up, standardised data on disability and functional limitation was included to derive a measure of healthy ageing (Ebrahim and Kalache 1996).

All deaths and cancer registrations are flagged (NHSCR) and added to the database. The research from the MRC Caerphilly Prospective Study has already resulted in around 150 publications and this will continue to increase as currently there are three funded research projects in progress.

Source: <http://www.bris.ac.uk/social-community-medicine/projects/caerphilly/about/>

Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS)

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Baseline data were obtained from the Caerphilly Study Archive, Department of Social Medicine, Bristol University, UK.

Accepted 22 August 2011

ABSTRACT

Background Benzodiazepine use is widespread in older people, although its benefit is uncertain.

Aim To investigate the long-term effect of benzodiazepine use upon dementia risk.

Methods A prospective cohort of men seen on five occasions over 22 years with full medication histories, repeat measures of cognitive function and a clinical diagnosis of dementia.

Results Of 1134 men with complete data, 103 (9.1%) had been taking benzodiazepines regularly at one or more phases. These men showed a marked increased incidence of dementia (OR=3.50, 95% CI 1.57 to 7.79, $p=0.002$), which persisted despite adjustment for psychological distress and other covariates. Men exposed in earlier phases showed a greater association than more recent exposure, counter to what one would expect if this was due to reverse causation, though we failed to demonstrate a dose–response effect with drug duration.

Conclusion The taking of benzodiazepines is associated with an increased risk of dementia.

use in older persons,^{1 12} which may persist for over 6 months after withdrawal of medication.¹³ Further evidence is therefore required to establish whether benzodiazepine use has any long-term adverse cognitive implications. In the present study, we report the first long-term prospective evidence on the association between benzodiazepine use and risk of dementia.

METHODS

Sample

The Caerphilly Prospective Study is based on a representative population sample of men born between 1920 and 1939, resident in a typical small town in South Wales. The men were first seen between 1979 and 1983 when aged 45–64 years. The initial response rate was 89%, and the survivors have been re-examined on four occasions: 1983–1988, 1989–1991, 1993–1995 and 2002–2004 (phases 2–5). Ethical approval has been obtained for each phase of the study with the most recent approval being obtained from the South East Wales Research Ethics Committee.

Assessment

Complete lists of drugs taken ‘regularly’ by each man were recorded at each examination. Two measures of benzodiazepine use are used in what follows: first, the reporting of the use of the drug at any phase of the study. Second, an estimate of the likely duration of use of the drug was made by identifying men who reported its use at only one examination (referred to as ‘4 years or less’ in what follows) and those who reported its use at two or more examinations (referred to as ‘>4 years’).

In phase 3, when the men were aged 55–74 years, several tests of cognitive function, including the AH4, National Adult Reading Test (NART) and four choice reaction time task, the Mini-Mental State Examination (MMSE) and Cambridge Cognitive Examination (CAMCOG), were completed by each man.¹⁴ The AH4 is a test of fluid IQ, while NART is a test of crystallised IQ and is considered to estimate premorbid cognitive ability. The MMSE and CAMCOG are tests of global impairment. Each man also completed the General Health Questionnaire (GHQ-30),¹⁵ and the standard cut-off of a score of >4 was used as an indication of psychological distress, which involves both anxiety and depression. Data on trait anxiety¹⁶ were also available from the examination 5 years prior to this (phase 2), and we have used a log-transformed anxiety score due to its skewed distribution. Data were also collected at

INTRODUCTION

With the ageing of the population, dementia has become a major public health problem. Many drugs, and especially benzodiazepines, are believed to cause cognitive impairment, yet the use of these drugs appears to be widespread. Puustinen *et al*¹ found that ‘nearly every second patient’ in an acutely hospitalised population in Finland were taking benzodiazepines, and Paterniti *et al*² estimated that >1 million French people aged 60 years and older are chronic users. In the UK, 11.7 million prescriptions were issued for benzodiazepines in 2007.³ Published evidence on the relationship between benzodiazepines and cognitive decline or dementia is inconsistent. While a number of studies report an increase in cognitive decline in benzodiazepine users,^{2 4} others find no such evidence.^{5 6} Evidence on dementia is more limited. Two small prospective studies found no evidence of harm over 3 and 5 years, respectively,^{7 8} while two case–control studies report an increased risk of dementia with benzodiazepine use.^{9 10} In a review of the evidence, Verdoux *et al*¹¹ commented on the ‘discrepant findings’ on the risk of cognitive decline and concluded that ‘the hypothesis that long-term exposure to benzodiazepines may induce permanent brain damage is merely speculative’. A third strain of evidence comes from pharmacological studies that have identified acute adverse cognitive effects of benzodiazepine

phase 3 for a number of aspects of sleep, including daytime sleepiness.¹⁷

In the fifth examination, the men being aged 65–84 years, tests of cognitive function were repeated, and those men who had a score of <83 on the CAMCOG or a decline in CAMCOG score of ≥10, together with subjects who failed to complete the CAMCOG, were selected for a clinical assessment (by MF).¹⁸

Full details of the clinical assessment of the selected men are reported elsewhere.¹⁸ In brief, this included a modified CAMDEX interview of subject and informant,¹⁹ the Rosen-revised Hachinski Ischaemic score,²⁰ neurological examination with Frontal Assessment Battery,²¹ Clinical Dementia Rating²² and the Informant Questionnaire on Cognitive Decline in the older people.²³ Available medical records were reviewed for details of relevant medical history, evidence of functional impairment due to cognitive impairment and results of neuro-imaging and other relevant investigations.

Subjects diagnosed with vascular dementia fulfilled the NINCDS-AIREN criteria for possible or probable vascular dementia.²⁴ Subjects were classified as non-vascular dementia if they fulfilled DSM-IV criteria for dementia²⁵ and had no clinical features to suggest cerebrovascular disease operationalised as a Hachinski Ischaemic score ≤2 and an absence of cerebral infarction or significant white matter change on available neuroimaging. Most of these subjects fulfilled the NINCDS-ADRDA criteria for probable Alzheimer’s disease,²⁶ but due to small numbers, all non-vascular conditions were combined in the analyses which follows. Subjects who had screened positive but with insufficient impairment to warrant dementia diagnosis on clinical assessment were classified as cognitive impairment not dementia (CIND).

Analysis

We first present the relationships between benzodiazepine taking at any phase of the study and the subsequent development of dementia. We present ORs (95% CIs and p values) from a logistic regression model adjusted for confounding at baseline by age, social class, education, smoking, cardiovascular disease and at phase 3 of the study for a number of cognitive tests as factors that may determine both risk of dementia and use of benzodiazepines. Three further models were tested with further adjustment for psychological distress, trait anxiety and daytime sleepiness and more proximal determinants of benzodiazepine use. We investigated a dose–response relationship by grouping men according to duration of drug use as defined above. To investigate reverse causation, that is, that any association between benzodiazepines and dementia reflects premorbid changes that increase the risk of being prescribed benzodiazepines secondary to the disease process, we repeated the analyses comparing more recent exposure to benzodiazepines, within 12 years of outcome (phases 4 or 5) with earlier exposure and between 13 and 22 years prior to outcome (phase 1, 2 or 3). If associations are due to reverse causation, we would hypothesise that associations would be stronger for more recent exposure than past exposure.

RESULTS

At the time of the most recent re-examination of the Caerphilly cohort, there were 1634 surviving eligible men of whom 1134 (70%) provided complete data and are the subject of this analysis. One hundred and three men (9.1%) reported taking benzodiazepines regularly at some time. Of these, 41 men reported benzodiazepine use at only one phase of the study

(shown as ‘≤4 years’) and 62 men reported at more than one phase (shown as ‘>4 years’). Mean follow-up was 22 years (range 19–24 years).

Men who were not followed were more likely to be older, have manual occupations, hold no educational qualifications and be current smokers at baseline (table 1). They were less likely to be married and slightly more anxious, although less likely to use benzodiazepines. Not followed men had poorer cognitive function. The differences in age and marital status were small. No difference in psychological distress was detected.

A comparison between men who had and had not taken benzodiazepines found men who took benzodiazepines were more likely to be psychologically distressed and have higher levels of trait anxiety and daytime sleepiness and a slightly lower body mass index (table 2). Men who had ever taken benzodiazepines had slightly worse cognitive function performance except for the NART score. Although there was no association of NART with benzodiazepine use, there was an association of education with benzodiazepine use.

When the men were aged 65–84 years, 268 (24%) were selected by the criteria described above for a clinical examination and 93 were found to have dementia (table 3). In 44 of the men with dementia, this was judged to be due to vascular disease processes, and in 49, the dementia was judged to be due to non-vascular disease, mostly Alzheimer’s disease. There were associations for both vascular dementia (OR=3.10, 95% CI 0.98 to 10.72) and non-vascular dementia (OR=3.34, 95% CI 1.10 to 10.18). In contrast, there was no evidence of an association with CIND (OR=0.63, 95% CI 0.27 to 1.48). Further adjustment for psychological distress, trait anxiety and daytime sleepiness had little effect on these associations, although NART score was not related to dementia independently of benzodiazepine use.

No evidence for a dose–response relationship was found (table 4). Men who were exposed to benzodiazepines for ≤4 years showed a much higher risk of dementia (OR=4.38, 95% CI 1.15 to 16.75) than those who took them for >4 years (OR=2.31, 95% CI 0.74 to 7.20). This pattern was found for both vascular and non-vascular dementia.

Evidence for reverse causation was sought by comparing earlier (13–22 years prior to outcome: study phases 1, 2 and 3) and more recent benzodiazepine use (within 12 years of outcome: study phases 4 and 5) (table 5). A recency effect was not found. For earlier use of benzodiazepines, evidence of an association was strongest for non-vascular dementia (OR=4.19,

Table 1 Sample characteristics according to follow-up status

Variable	Phase 2 followed	Phase 2 not followed	p Value
Age in years, mean (SD)	56.1 (4.4)	57.6 (4.5)	<0.001
Log alcohol: ml/wk, mean (SD)	4.28 (1.43)	4.15 (1.52)	0.03
State anxiety, mean (SD)	35.9 (8.9)	37.4 (9.4)	<0.001
Fluid intelligence, mean (SD)	26.7 (10.7)	22.5 (10.9)	<0.001
Choice reaction time: msec, mean (SD)	0.872 (0.22)	0.931 (0.24)	<0.001
NART, mean (SD)	25.12 (12.0)	21.13 (11.4)	<0.001
MMSE, mean (SD)	26.68 (2.5)	26.1 (2.7)	<0.001
CAMCOG, mean (SD)	90.4 (7.2)	88.4 (7.3)	<0.001
Benzodiazepine used, %	7.5	3.9	<0.005
Ischaemic Heart Disease free, %	75	64	<0.001
Manual social class, %	62	73	<0.001
Married, %	90	85	<0.001
No educational qualification, %	45	58	<0.001
Current smokers, %	36	52	<0.001
Psychological distress present, %	21	23	NS

Table 2 Use of benzodiazepines and possible confounding factors at baseline

Variable	Use of benzodiazepines		Difference (95% CI)	p Value
	103 men taking benzodiazepines at any phase	1085 men never used benzodiazepines		
Age, mean (SD)	61.7 (4.6)	61.2 (4.4)	0.5 (−0.5 to 1.4)	0.31
Alcohol >20cc/day, %	26.5	28.2	−1.7 (−10.9 to 7.5)	0.72
Log anxiety, mean (SD)†	3.73 (0.24)	3.53 (0.24)	0.20 (0.15 to 0.25)	<0.001
AH4, mean (SD)	24.1 (10.2)	27.0 (10.7)	−2.9 (−5.1 to −0.7)	0.02
MMSE, mean (SD)	26.08 (2.57)	26.73 (2.47)	−0.65 (−1.20 to −0.11)	0.02
NART, mean (SD)	25.4 (12.3)	25.1 (11.9)	0.3 (−2.4 to 2.9)	0.84
CRT, mean (SD)	0.94 (0.21)	0.87 (0.21)	0.07 (0.03 to 0.12)	0.002
CAMCOG, mean (SD)	88.8 (8.4)	90.6 (7.1)	−1.81 (−3.58 to −0.04)	0.02
IHD free, %	66.0	76.1	−10.1 (−19.6 to −1.0)	0.019
Manual social class, %	64.7	59.8	4.8 (−5.0 to 14.7)	0.35
Married, %	85.4	90.8	−5.3 (−12.4 to 1.7)	0.08
No educational qualification, %	53.8	44.2	9.6 (−0.75 to 19.95)	0.07
Current smokers, %	29.3	28.8	0.5 (−8.9 to 9.9)	0.91
Psychological distress present, %*	40.7	20.3	20.4 (9.7 to 31.1)	<0.001

*'Distress' implies a score on the General Health Questionnaire score of >4 (see text).

†The anxiety score is the log-transformed Spielberg questionnaire score (see text).

NART, National Adult Reading Test; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; CRT, Choice Reaction Time; IHD, Ischaemic Heart Disease.

95% CI 0.90 to 19.49). Raised ORs were also found for later use, but these were smaller than for earlier use and, possibly due to small numbers, statistical significance was not achieved. Counter to a reverse causation hypothesis, the association between benzodiazepine use and dementia was stronger with a longer latency period than for those men who had commenced therapy more recently.

DISCUSSION

In a representative population sample of men with high follow-up rates over 22 years, the risk for dementia associated with the use of benzodiazepines is high and if causal would be alarming for what may be an iatrogenic cause. Although an element of reverse causality cannot be totally excluded, this is unlikely to be a complete explanation as there was only a modest difference in cognitive function when assessed at phase 3 of the study; the association was sustained once men with more recent exposure to benzodiazepines were excluded and the ORs were more marked for men only exposed in earlier than later phases of the study.

We observed little evidence that our association differed by whether the dementia was thought to be of vascular as compared with non-vascular origin. This may reflect difficulties in clinically differentiating these subtypes, and it is well recognised that mixed dementia with both Alzheimer's and vascular pathology is under diagnosed. Prior reports have noted

a reduction in benzodiazepine receptors in various brain regions at autopsy of Alzheimer's disease patients.²⁷

Previous literature

It is difficult to compare the results we present with those in the literature. First, most of the published studies relate benzodiazepine taking to cognitive decline and not to clinical dementia. In fact, if we ignore the distinction between dementia and CIND in our data, the adjusted OR with benzodiazepine taking which we obtain is 1.60 (95% CI 0.88 to 2.92). This finding is reasonably similar to the findings of Paterniti *et al*² in a prospective 4-year study (OR 1.9, 95% CI 1.0 to 3.6). A number of other retrospective case-control studies reported finding no significant effect on cognitive function.^{1 4 6}

Only a few studies appear to have reported on dementia, rather than cognitive decline. Lagnaoui *et al*⁹ conducted a case-control study with 150 patients with dementia and reported an OR of 2.3 (95% CI 1.2 to 4.5) for the use of benzodiazepine. Wu *et al*¹⁰ compared benzodiazepine use in a case-control study of 779 patients with dementia and reported an OR of 2.37 (p<0.001) in subjects who had taken benzodiazepine for >180 days within a 1-year period, together with a significant relationship between dementia and the cumulative dose of the drug taken. On the other hand, Fastbom *et al*⁷ followed a sample of 242 subjects with low cognitive function test results for 3 years and found a

Table 3 OR for dementia and for cognitive impairment not dementia (CIND) in men who reported taken benzodiazepine compared with those who reported never taking the drug

ORs adjusted for	Clinical dementia 93 men, 22 on benzodiazepine	CIND 175 men, 13 on benzodiazepine	'Vascular' dementia 44 men, 12 on benzodiazepine	'Non-vascular' dementia 49 men, 10 on benzodiazepine
Age, social class, smoking, alcohol intake, Education, BMI, angina, IHD and NART, MMSE, AH4, CRT, CAMCOG at baseline	3.10 (1.33 to 7.23), p=0.009	0.63 (0.27 to 1.48), p=0.29	3.24 (0.98 to 10.72), p=0.05	3.34 (1.10 to 10.18), p=0.03
Above, plus distress	3.10 (1.28 to 7.51), p=0.01	0.65 (0.27 to 1.56), p=0.33	3.20 (0.90 to 11.39), p=0.07	3.72 (1.15 to 12.04), p=0.03
Above, plus anxiety	2.98 (1.18 to 7.55), p=0.02	0.57 (0.23 to 1.43), p=0.23	3.39 (0.87 to 13.16), p=0.08	3.50 (1.02 to 11.97), p=0.05
Above, plus daytime sleepiness	2.94 (1.16 to 7.46), p=0.02	0.58 (0.23 to 1.45), p=0.25	3.61 (0.91 to 14.30), p=0.07	3.59 (1.04 to 12.36), p=0.04

BMI, body mass index; NART, National Adult Reading Test; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; CRT, Choice Reaction Time; IHD, Ischaemic Heart Disease.

Table 4 OR for cognitive impairment in 93 men by estimated duration of taking benzodiazepine

Estimated duration of benzodiazepine taking	All dementia 93 men	'Vascular' dementia 44 men	'Non-vascular' dementia 49 men
4 years or less	10 men	4 men	6 men
OR (95% CI), p	4.38 (1.15 to 16.75), 0.03	2.96 (0.25 to 35.71), 0.39	6.61 (1.42 to 30.83), 0.02
>4 years	12 men	8 men	4 men
OR (95% CI), p	2.31 (0.74 to 7.20), 0.15	3.83 (0.86 to 17.11), 0.08	1.86 (0.31 to 10.96), 0.50

ORs have been adjusted for age, social class, education, smoking, alcohol intake, body mass index, angina, IHD, cognitive function (NART, CAMCOG, AH4, MMSE, CRT), distress, anxiety and daytime sleepiness.

NART, National Adult Reading Test; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; CRT, Choice Reaction Time; IHD, Ischaemic Heart Disease.

reduced incidence of dementia in those who used benzodiazepine (9%) compared with the incidence in non-users of the drug (23%).

The division we make by duration of drug taking is crude, and yet a difference in the incidence of dementia was found, and is consistent with the previous finding of Lagnaoui *et al.*,⁹ who found a higher risk of dementia in former (OR=2.3, 95% CI 1.2 to 4.5) than current (OR=1.0, 95% CI 0.6 to 1.6) benzodiazepine users. One would normally expect to see a positive dose-response relationship so that greater duration of exposure is associated with greater risk, but a contrary pattern shown by two studies deserves closer attention.

Strengths and limitations

The main strength of our data comes from their prospective nature and the long follow-up period of 22 years. This period is more than double the duration of all previous studies. In addition, we were able to control for the major confounders (depression and anxiety), which are strong determinants of benzodiazepine prescribing behaviour as well as risk factors for dementia. Further adjustment was also made for socioeconomic indicators (social class, education, marital status). Drug taking was carefully and repeatedly recorded at each 5-year phase of the study, although the reasons for prescribing benzodiazepines was not recorded, and dementia was diagnosed clinically at the end of the follow-up period by two observers, who were blind with regard to previous drug taking habits removing any possibility of recall or observer bias. A major limitation of the study is, however, the small number of subjects who reported the taking of benzodiazepine and hence our relatively imprecise estimates of risk. The division into vascular and non-vascular dementia is known to have considerable uncertainty when validated against postmortem verification.²⁸ Nevertheless, we have already shown within the same cohort of men that sleep disturbance, anxiety and haemostatic factors are differentially predictive of the two types of dementia.²⁹⁻³¹

Interpretation

We think it is unlikely that reverse causation (also known as 'protopathic bias') explains our findings and believe that these

data are cause for concern. Although evidence of an association with recent benzodiazepine use was found, indicating an effect of prodromal or early dementia on benzodiazepine prescribing, this did not account for the association of dementia with benzodiazepine exposure 13-22 years prior to outcome. Furthermore, apart from the modest differences in cognitive function at phase 3 of the study, NART score, which is an estimate of premorbid cognitive function, did not show a difference with benzodiazepine exposure, hence making 'confounding by indication' unlikely. Although measures of sleepiness and psychological state were not available at baseline, when adjustment was made for daytime sleepiness and psychological state assessed at phase 3 of the study, no attenuation of effect was found. The absence of an association with CIND requires consideration. It either suggests that the association with dementia is spurious or that any harm due to benzodiazepine use was advanced at the point of CIND assessment. This latter explanation would be consistent with finding of an association of dementia with earlier benzodiazepine use.

It is possible that this is a chance phenomenon or due to residual confounding, although where numbers allowed, the associations found were reasonably strong and adjustment was made for socioeconomic indicators. An alternative explanation is that men who are more sensitive to drug-related side effects (and who stop taking benzodiazepines after a short time) are either more susceptible to dementia or their risk of dementia is increased due to benzodiazepines. Men who do not experience detectable side effects of the drug, however, are either less susceptible to dementia or suffer less cerebral harm from taking the drug. In this case, benzodiazepines may either be a pharmacological biomarker or a causal agent for dementia or both.

Conclusions

In conclusion, we have provided long-term prospective evidence of a possible adverse effect of benzodiazepines on the development of dementia. This is consistent with previous findings on dementia but is based on a far greater follow-up period reducing the likelihood of reverse causation. This association was

Table 5 OR for dementia according to benzodiazepine use in phase of study

Estimated duration of benzodiazepine taking	All dementia	'Vascular' dementia	'Non-vascular' dementia
Men on benzodiazepines at phases 1, 2 and 3 (excluding men on benzodiazepines at phases 4 and 5)	12 men	6 men	6 men
OR (95% CI), p	2.64 (0.71 to 9.78), 0.15	1.45 (0.13 to 16.27), 0.76	4.19 (0.90 to 19.49), 0.07
Men on benzodiazepines at phases 4 and 5	10 men	6 men	4 men
OR (95% CI), p	2.44 (0.78 to 7.57), 0.12	4.25 (0.94 to 19.17), 0.06	2.03 (0.38 to 10.75), 0.40
Men on benzodiazepines at phase 5	7 men	3 men	4 men
OR (95% CI), p	2.64 (0.64 to 10.97), 0.18	3.31 (0.42 to 25.96), 0.26	3.47 (0.61 to 19.85), 0.16

ORs have been adjusted for age, social class, education, smoking, alcohol intake, body mass index, angina, IHD, cognitive function (NART, CAMCOG, AH4, MMSE, CRT), distress, anxiety and daytime sleepiness.

NART, National Adult Reading Test; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; CRT, Choice Reaction Time; IHD, Ischaemic Heart Disease.

What is already known on this subject

Benzodiazepines are prescribed widely for older people and can affect cognitive function. The effect of benzodiazepines on dementia is unclear due, in part, to a dearth of long-term follow-up data.

What this study adds

From this study, we know that benzodiazepine use is associated with dementia in the long term (22 years) and that this is unlikely to be due to protopathic bias or confounding by indication. The absence of a dose (duration)—response relationship suggests that any effect is limited to a susceptible subgroup rather than widespread. Whether benzodiazepines are an iatrogenic cause of dementia or a biomarker for dementia risk is unclear. These findings indicate that great care should be taken upon the beginning of benzodiazepines with middle-aged and older people.

observed for both vascular and non-vascular dementia. Given the widespread use of these drugs and the ageing population, it is important that other studies with better data on the determinants of benzodiazepine prescribing, side effects and reasons for drug cessation examine this association. Furthermore, it is important to examine if these associations are specific for benzodiazepines or are seen with other types of hypnotic drugs or anxiolytic therapies. In view of the evidence now available, it is doubtful if randomised trials of benzodiazepine would be ethically acceptable.

Acknowledgements We would like to thank Truda Bell and her field team for their excellent work in collecting these data along with members of the cohort for their generous co-operation.

Funding This work was funded by the Alzheimer's Society. The Caerphilly Study was initiated by the former MRC Epidemiology Unit (South Wales) and was funded by the Medical Research Council of the United Kingdom.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was approved by South east Wales Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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There are 2 additional points which I would like the committee to consider;-
Our RCN members tell us how difficult it is to get study leave even for mandatory training. This is reflected in the staff survey. It would be great if there was stroke education available in Wales but we would have to be mindful how difficult it would be for nurses to attend.

I believe when talking about stroke prevention we have to consider the prevention messages in the other Service Development Plans and consider the same prevention messages which span stroke, cardiac and diabetes.

During the evidence session, you noted that Professor Marcus Longley, of the Welsh Institute of Health and Social Care (WIHSC), has agreed to work with the Stroke Association to develop an economic assessment of stroke services in Wales. You also noted that the National Institute for Social Care and Health Research Clinical Research Centre (NISCHR–CRC) has indicated that funds are available to undertake the assessment and you agreed to present this work to the Committee on completion. It would be helpful if you could indicate when this is likely to be.

I'd like to emphasise that we are due to hold an initial exploratory meeting with Professor Longley to agree how we can take this piece of work forward. We have had a conversation, on an enquiry basis with NISCHR who have indicated that the study would fit into their funding programme. However, at this stage the conversations are exploratory and no commitments are yet made. Of course we will be very pleased to share the development and outcome of this work as and when it is ready and appropriate to do so.



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Bwrdd Iechyd
Aneurin Bevan
Health Board

Ref: JS/LM/sm

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11 November 2013

FAO Llinos Madeley, Committee Clerk
Health and Social Care Committee
National Assembly for Wales
Cardiff Bay
CF99 1NA
HSCCommittee@wales.gov.uk

Dear Ms Madeley,

Re. Stroke risk reduction follow-up inquiry 2013, Additional Information

During the Health and Social Care Inquiry of 23rd October Panel 3 – LHB and Public Health Wales evidence session - the chair asked for additional information on the cost of the Welsh Cardiac and Cancer Networks to be submitted as additional information. Please therefore find below a brief overview of the Networks and their running costs.

CARDIAC NETWORKS

There are two Cardiac Networks in Wales: the South Wales Cardiac Network, covering 6 Health Boards, was formed in 2011 through the merger of two former Regional Networks; and the North Wales Cardiac Network which is coterminous with Betsi Cadwaladr University Health Board. Both Networks engage their local Health Boards, WAST and Public Health Wales, and work in partnership with stakeholders including WG, WHSSC, LMCs, other clinical networks, CHCs, other patients groups and the voluntary sector.

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Bwrdd Iechyd Aneurin Bevan yw enw gweithredol Bwrdd Iechyd Lleol Aneurin Bevan
Aneurin Bevan Health Board is the operational name of Aneurin Bevan Local Health Board

The South Wales Network is hosted and chaired by Aneurin Bevan University Health Board. The North Wales Network is integral to Betsi Cadwaladr University Health Board.

The Networks provide support to their Health Boards in the development of cardiac services to meet the Cardiac Disease National Service Framework and Quality Requirements, and more recently the newly published Heart Disease Delivery Plan. Their core functions are to provide consistent clinical oversight and ownership of service planning and developments; to highlight inequity and gaps in service and to support improvement actions; to gather, disseminate and promote evidence based practice; and to support Health Boards to achieve the benefits of their integrated structure across the patient pathway from primary to tertiary care.

Due to the integral nature of the North Wales Network to Betsi Cadwaladr University Health Board and the cross border pathways of North Wales patients, the Network has a lead role in managing service development and significant projects (e.g. 2nd Cardiac Catheter Laboratory at YGC), writing and developing all cardiac business plans, as well as writing the Heart Disease Delivery Plan on behalf of the Health Board. Additionally, the Network is responsible for leading the Health Board's Repatriation Plans working closely with Operations to monitor and manage repatriated activity and monitoring contracts with English providers.

The South Wales Cardiac Network is now providing the secretariat for the all Wales Heart Disease Implementation Group and is working with Welsh Government to co-ordinate the Strategic Action Plan for that Group.

Cardiac Network Funding

The annual funding for the South Wales Cardiac Network, agreed in 2011/12 by the Welsh Assembly Government, is £326,226 pa.

The annual funding for the North Wales Cardiac Network, agreed in 2011/12 by the Welsh Assembly Government, is £157,311 pa.

This funding covers the employment and functioning of the Network core team of employed staff and clinical leads, together with non staff Network costs. There is no specific funding for service developments or improvement initiatives. Since reorganisation in July 2011 the funding for the South Wales Network has been included within Aneurin Bevan Health Board budget.

CANCER NETWORKS

There are two Cancer Networks in Wales: the South Wales Cancer Network, covering 6 Health Boards and Velindre NHS Trust, which was formed in 2011 through the merger of two former Regional Networks; and the North Wales Cancer Network which is coterminous with Betsi Cadwaladr University Health Board. Both Networks work in partnership with their Health Boards and Trusts, Community Health Councils, Voluntary Organisations and Public Health Wales to

co-ordinate the planning, organisation and delivery of cancer services in their areas.

The South Wales Network is hosted and chaired by Abertawe Bro Morgannwg University Health Board. The North Wales Network is integral to Betsi Cadwaladr University Health Board.

The Networks provide support to their Health Boards and Trusts in the development of cancer services to meet the quality requirements of the National Cancer Standards, and more recently the newly published Cancer Delivery Plan. Their core functions are to provide consistent clinical oversight and ownership of service planning and developments; to highlight inequity and gaps in service and to support improvement actions; to gather, disseminate and promote evidence based practice; and to support Health Boards to achieve the benefits of their integrated structure across the patient pathway from primary to tertiary care. The Cancer Networks are also currently working with Health Inspectorate Wales on the development of standards for peer review and systems for implementation which will be used by HIW to inform similar systems in other disease specific networks.

The North Wales Network has a lead role in managing local service developments and the commissioning of specialist services from English providers.

Cancer Network Funding

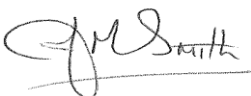
The core annual funding for the South Wales Cancer Network, agreed in 2011/12 by the Welsh Assembly Government, is £368,000 pa.

The annual funding for the North Wales Cancer Network, agreed by the Welsh Assembly Government, is £125,000 pa.

This funding covers the employment and functioning of the Networks core teams of employed staff and clinical leads, together with non staff Network costs. There is no specific funding for service developments or improvement initiatives which is sought through business case or bidding processes to number sources. Since reorganisation in 2011 the funding for the South Wales Network has been included within the Abertawe Bro Morgannwg University Health Board budget.

I trust the above meets your requirements but please do not hesitate to contact me should you require clarification or any further information.

Yours sincerely



J M Smith
Executive Director of Therapies and Health Science
Aneurin Bevan Health Board

