Health and Social Care Committee

Meeting Venue:
Committee Room 1 - Senedd

Meeting date:
21 November 2013

Meeting time:
09:25

Cynulliad Cenedlaethol Cymru
National Assembly for Wales

For further information please contact:

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Agenda

Pre-Meeting (09.25-09.30)

1 Introductions, apologies and substitutions (09:30)

2 General scrutiny session with the Chief Dental Officer (09:30 - 11:00) (Pages 1 - 24)

Witnesses:

David Thomas - Chief Dental Officer

Lisa Howells - Senior Dental Officer

3 Papers to note (11:00) (Pages 25 - 42)

Additional information submitted to the follow-up inquiry on stroke risk reduction following the session on 23 October (Pages 43 - 80)

Letter from the Minister for Health and Social Services - measles single vaccine provider (Page 81)

Letter from the Minister for Health and Social Services - unscheduled care plans and formal winter plans (Pages 82 - 83)

4 Motion under Standing Order 17.42 to resolve to exclude the public from the remainder of the meeting (11:05)

BREAK (11.05 – 11.15)

5 General scrutiny session with the Chief Dental Officer – private discussion to consider evidence (11:15 – 11:30)

6 Consideration of the key issues arising from the Committee's follow-up inquiry on stroke risk reduction (11:30 – 11:45) (Pages 84 - 93)

7 Consideration of the key issues arising from the Committee's scrutiny session on unscheduled care – preparedness for winter 2013/14 (11:45 – 12:00) (Pages 94 - 106)

8 Committee remit (12:00 – 12:15) (Pages 107 - 116)

Document is Restricted

Health & Social Care Committee

Date: Thursday 21 November 2013

Venue: National Assembly for Wales

Title: Access to NHS dentistry

Purpose

1. The Health and Social Care has been discussing its forward work plan for the Spring term and identified access to NHS dentistry as a possible area for conducting a future inquiry.

2. The Committee has requested an evidence paper on the issues for its general scrutiny session on 21 November, to be attended by the Chief Dental Officer David Thomas.

Background

3. In looking at the challenges regarding access and the changes made to the dental system, it is important to remember the level of change there has been in dental need and demand since the NHS dental service began in 1948. In the immediate post war years NHS dentistry served a nation with generally poor oral health, large amounts of untreated decay and therefore with extensive treatment requirements. A large proportion of the adult population were toothless (edentate). As recently as 1973, 40% of the population had no natural teeth.

4. The NHS dental system set up in 1948 reflected a world where those with teeth typically needed complex treatment for extensive decay and those without required full dentures. From the early 1970s onwards developments in dental care and particularly the spread in the use of fluoride toothpaste has meant that an ever-increasing proportion of adults retain their teeth into old age. The latest Adult Dental Health Survey (ADHS) published in 2011 found that only 10% of the adult population in Wales were edentate. The majority of these were aged 75 and over. Decay rates had fallen in all groups (although there remains a marked gap between socio economic groups – Annex 1 Table A).

5. Over the past two decades or so patients' focus has moved from simply ensuring their teeth are healthy and pain-free to an ever-stronger desire that they should also be cosmetically pleasing. This presents new challenges about where the boundaries should lie between clinically needed treatment—available for all who want it from the NHS - and purely cosmetic treatment, which most would agree need not necessarily be delivered by the NHS.

6. The system set up in 1948 was provider and treatment driven. Dentists decided on the level and location of services, and under payment per item of service the more treatment delivered and the more complex that treatment was, the more the dentist earned. NHS dental charges were introduced in 1951 for charge paying adults (those under 18, or in receipt of certain benefits or pregnant are exempt from all charges). Charges were based on individual items of service.

7. From the early 1990s, the inherent risks of a provider driven system that left dentists to decide where and what level of service should be available became apparent. As dentists drifted away from the NHS, service commissioners had no powers to seek alternative providers. The access difficulties that resulted, the legacy of which we are still dealing with today, are well known. The incentive to deliver complex restorative treatment was a good fit for a nation in poor oral health but an increasingly bad fit as decay rates declined. Dentists complained of being on a treadmill that allowed no time for preventive as well as restorative treatment.

8. In October 2004 the National Institute for Health and Social Care Excellence (NICE) introduced guidelines on the recall interval between routine dental examinations. Largely because the oral health of the nation has improved dramatically over the last few decades, routine visits to the dentist every six months are not necessary for everyone anymore. Everyone needs regular visits to the dentist but the interval between visits can vary depending upon the clinical need of the patient (up to a year between visits for children and up to two years for adults).

9. The April 2006 dental reforms created much greater stability in funding and access, with the local NHS for the first time having local control of dental resources. Local Health Boards (LHBs) use this money to agree local contracts with dentists and, if a dentist leaves the NHS, can use the released funds to bring in new services.

10. The main gains have been at local level. Some previously very hard-pressed areas have seen significant improvements in access for local people. Hywel Dda, Betsi Cadwaladr and Powys LHB areas have seen particular successes in addressing long standing access issues.

Headline activity and need data

11. In March 2006, immediately prior to the new contract, 50.7% of the population were registered with a dentist. Since 2006 access to ‘high street’ NHS dental services has remained broadly stable with some 54-55% of the population regularly accessing NHS dental care. However, the number of individual patients has increased by over 30,000 reflecting the rise in the population. There is still variation between LHB areas (Annex 1 – Table B) but this has reduced significantly from the position in the 1990s.

- 1.68 million patients were recorded as accessing NHS dental treatment in the 24 months to 31 March 2013. This amounts to 54.8 per cent of the population - 64.7 per cent of children (under 18 years) and 52.2 per cent of adults. This is an increase of some 8,500 over the same period in the previous year.
- In addition the Community Dental Service who work predominantly with young and vulnerable patients, had contact with 71,400 individual patients across Wales in 2011/12 (this figure is not included in the above totals of those accessing other NHS dental services).
- The latest workforce data for the year ending 31 March 2013 showed there were 1,392 dentists with NHS activity recorded, equating to 4.5 dentists per 10,000 population. This compares with 1,360 at 31 March 2012 and 1,087 at 31 March 2006.

- 89.9% of patients said they were satisfied with the dentistry they received. 84.2% of patients were satisfied with the time they had to wait for an appointment.
- Total dental spend (net) was £140.2m in 2012/13.

12. The ADHS found that 69% of dentate adults in Wales reported attending the dentists for regular check-ups; 7% reported attending occasionally; 23% reported attending only when they had trouble with their teeth; and 1% said they never attended. Overall 79% of dentate adults in Wales indicated that they attended the dentists at least every 2 years.

13. The oral health survey of 12 year olds carried out in 2008/09 found the percentage of 12 year old children affected by dental decay (i.e. those with at least one tooth decayed, missing due to decay or filled teeth) had fallen from 51% in 2001 to 42.5% in this latest survey.

14. Compared with 2007/08, the 2011/12 dental epidemiological survey of 5 year olds shows a 6% decrease in the proportion of children with experience of dental decay in Wales (47.6% falling to 41.4%). This is mirrored by statistically significant reductions in all Wales mean decay experience and active decay levels. Dental disease levels in children are improving in Wales across all social groups. There is no evidence of widening inequalities. This is in contrast with previous surveys when improved decay levels were normally associated with widening inequality.

15. The Welsh Citizen Survey of Dental Services 2009/10 asked why people had not contacted a dental practice in Wales in the last 2 years. The reasons given were:

No need	63%
Access services in England	9%
Difficult to get an NHS dentist	8%
Scared of/don't like dentists	7%
Could not obtain information to contact the practice	4%
Too expensive	3%

16. Overall 70% of dentate adults received either paid for or free NHS dental care (37% paid; 33% free), and 29% received private dental care. Total income from NHS patient charges in 2012-13 totalled £28.5m.

<u>Government commitment to NHS dental services</u>

17. There is a Programme for Government commitment to continue to increase access to NHS dental services where there are localised problems. In order to provide additional income to LHBs, NHS dental patient charges were increased from 1 September 2012 and 1 April 2013 - the first rise for six years. This will generate revenue of some £0.8m p.a. specifically for LHBs to finance improved and additional dental services.

18. There is evidence that some patients are still being recalled more frequently than is necessary and officials are working with LHBs and dental contractors to promote the application of current NICE guidance on dental recall intervals. This will help

provide an increase in capacity and guidance has been issued to LHBs aimed at ensuring effective delivery of NHS dental services and the management of contracts.

Delivery of NHS Orthodontic services

19. Demand for orthodontic treatment has increased across the UK, and undoubtedly there are some social and cultural factors involved. Demand can be raised by 'cosmetic' requests and can also be driven up by the presence of Specialist (High Street) providers themselves.

20. With the spending pressures facing the NHS, orthodontic provision has to be placed in context with other dental health priorities. Total expenditure on orthodontics within primary care dentistry already makes up a significant percentage of the total funding of dental services. It is therefore vital that continued funding is based upon sound needs assessment, prioritisation and an integrated approach between the orthodontic dental service providers.

21. Difficulties remain for patients seeking orthodontic treatment in some parts of Wales and there have been reports of lengthy waiting times for treatment. There are a number of reasons for this and LHBs have been working to address on-going capacity issues in both the secondary and primary care orthodontic services. In some instances list sizes are inflated through early, duplicate or inappropriate referrals and by other factors. Recruitment and retention has also been an issue for secondary care and specialist services in some rural areas.

22. In September 2009 an independent expert group, chaired by Professor Stephen Richmond, Professor of Orthodontics at Cardiff University School of Dentistry examined the provision of orthodontics in Wales. The review report reached some interesting and challenging conclusions.

23. In such difficult economic times it was encouraging that the report found current spending on orthodontics in Wales – over £13 million annually – is capable of largely meeting the orthodontic needs of Welsh patients. The review reported that the number of completed NHS orthodontic treatments for children was comprised of: 8,991 undertaken in general dental service; 1,620 in the Hospital Dental Service; and 420 in the Community Dental Service during the calendar year.

24. The report also made clear there is little unnecessary treatment undertaken, although there was a need for improved validation and further confirmation regarding the quality of services provided. The Health, Wellbeing and Local Government Committee reported in December 2010 on their own inquiry into orthodontic services in Wales. The Committee's recommendations supported our current policy direction and also mirrored the findings and recommendations of the expert group.

25. We have established a Strategic Advisory Group to produce an annual report on the provision of orthodontic services in Wales and to consider the recommendations of both the expert group and the Committee. We have issued guidance to help support LHBs and orthodontic providers to deliver more effective orthodontic services with Managed Clinical Networks (MCNs) being established in South West, South East and North Wales.

26. The development of MCNs is helping create a more efficient referral management process to reduce early, multiple and inappropriate referrals. LHBs are now using MCNs to identify patients who have been referred to more than one orthodontist or referred ahead of need to free up capacity; both of which have contributed in the past to the length of waiting lists.

Welsh Dental Pilot Programme

27. A previous Minister for Health and Social Services established a Task and Finish Group to review the dental contract introduced in 2006 and look at a range of issues to improve the way in which the contract works. A number of issues were of concern to the Task and Finish Group including the need to review and analyse the contract currency. It was concluded there was a need to pilot a number of new models which would look at alternative ways of working, improved quality, and changes to payment relating to the dental contract.

28. The Welsh Pilot programme has been established to test new systems of payment and delivery and to find a structure that will work for providers, LHBs and patients alike. We are piloting systems which move away from Units of Dental Activity as a means of specifying treatment categories and paying dentists, toward one which focuses on tailored patient care based on risk assessment and quality. Pilot providers are paid per patient on a weighted capitation basis, and practice performance is measured using a number of access and treatment-quality key performance indicators. The process has now been extended to run until March 2015.

29. Qualitative findings show practice staff and patients value the changes. In terms of evaluation this has been an on-going process. Miller Research Ltd is providing qualitative monitoring and evaluation. The quantitative monitoring and evaluation is being undertaken by Public Health Wales. A final evaluation report on the Pilots will be published in 2015.

Use of Direct Access to DCPs

30. Dental Care Professionals (DCPs) include dental therapists, hygienists and dental nurses. Until April 2013, treatment could only be carried out by a DCP on the prescription of a dentist. In May 2013 the General Dental Council (GDC) approved guidance which removed the necessity for patients to see a dentist before accessing certain treatments from DCPs. The GDC's 'Scope of Practice' guidance was reviewed and approved by the GDC in September 2013. The 2013 review allowed some additional scope of practice for all DCPs and clarifies the previous guidance. The GDC based their decision on a comprehensive literature review of over 100 research dental and other health-related papers. The review highlighted that there was no evidence of significant issues of patient safety resulting from the clinical activity of DCPs, and, that there was strong evidence that access to dental care improved as a result of direct access arrangements, of cost benefits to patients, and of high levels of patent satisfaction.

31. There is now a real opportunity for DCPs to carry out treatments without the prescription of a dentist. Many patients who are treated in CDS settings have high decay rates. These patients needs represent a significant portion of dentists' clinical time. Often recall intervals slip because of other patient priorities. A significant amount of time is spent monitoring oral hygiene, giving tooth-brushing instruction, discussing diet and applying topical fluoride, all of which are within the scope of practice of many DCPs.

32. In October 2013 the Minister for Health and Social Services approved a pilot study which will test direct access to dental care professionals in a CDS setting in Betsi Cadwaldwr and in Hywel Dda LHB areas.

Key priorities for future delivery of dental services in Wales

33. Dental services continue to be highly valued highly by patients and the imminent publication of Delivering Better Oral Health (our evidence based guidance developed jointly with Public Health England) will enable clinicians to adopt a more preventive approach to tackling dental disease within their practices. In addition we are working to develop a new contract for NHS primary care dental services. The engagement and enthusiasm we have seen from clinicians involved in the pilot process has been extremely encouraging and we need to continue this.

34. We are working with clinicians and commissioners to develop care pathways for patients in need of an element of advanced care. We need to ensure that we utilise the skills of the whole dental team within a specialist led, but not necessarily delivered, service that provides high quality care regardless of setting. Everyone understands the current financial climate is tight but we are committed to develop a system which produces dental services for patients, based on improving health outcomes, which are both cost effective and clinically effective and offering patients a positive experience of care in a safe environment.

35. The National Oral Health Plan "Together for Health: A National Oral Health Plan for Wales" was launched in March 2013. The five year Plan outlines how the key priorities and Programme for Government commitments in relation to oral health and dentistry will be met, and focuses on:

- the inequalities in oral disease and who is particularly at risk;
- how we can improve the effectiveness and efficiency of services;
- how to improve the quality of dental services to promote access;
- improving the efficiency of the current dental contractual arrangements; and health outcomes, in addition to providing excellent treatment

36. A key requirement of the Plan is for LHBs to develop Local Oral Health Plans (LOHPs) to address the oral health needs of their residents, ensuring effective commissioning and delivery of all dental services. LOHPs need to be submitted to Welsh Government by 31 December 2013.

Annex 1

Table A
Characteristics of dentate adults by socio-economic classification

	Characteristics of dentate adult				
Socio-economic classification of household	No. of natural teeth (Mean)	Presence of bleeding (Yes %)	Frequency of brushing (>= Twice a day)	Smoking status (% who smoke)	Presence of plaque (Yes %)
Managerial & professional	25.3	47	79	14	67
Intermediate occupations	23.5	57	64	27	77
Routine & Manual	23.7	61	66	32	85

Source: Adult Dental Health Survey 2009

Table B
NHS patients treated: adults and children by Local Health Board – 2 years ending 31.3.13

	Number of patients treated	% of patients treated	Number of adults treated	% of adults treated	Number of children treated	% of children treated
Wales	1,684,427.00	54.8	1,276,175.00	52.2	408,252.00	64.7
Betsi Cadwaladr University Health Board	350,565.00	50.8	264,237.00	48	86,328.00	61.6
Powys Health Board	80,295.00	60.4	64,074.00	59.8	16,221.00	62.9
Hywel Dda Health Board	172,765.00	45.1	129,157.00	41.9	43,608.00	58
Abertawe Bro Morgannwg University Health Board	322,343.00	62.1	245,448.00	59	76,895.00	74.1
Cwm Taf Health Board	171,228.00	58.1	136,133.00	58.7	35,095.00	56.2
Aneurin Bevan Health Board	325,579.00	56.3	244,454.00	53.9	81,125.00	65
Cardiff and Vale University Health Board	261,652.00	55	192,672.00	51.2	68,980.00	69.8

Source: StatsWales

Agenda Item 3

Health and Social Care Committee

Meeting Venue:	Committee Room 3- Senedd
Meeting date:	Thursday, 7 November 2013
Meeting time:	09:30 - 14:00

Cynulliad Cenedlaethol Cymru
National Assembly for Wales

This meeting can be viewed on Senedd TV at:
http://www.senedd.tv/archiveplayer.jsf?v=en_400000_07_11_2013&t=0&l=en
http://www.senedd.tv/archiveplayer.jsf?v=en_400001_07_11_2013&t=0&l=en

Concise Minutes:

Assembly Members:	David Rees (Chair) Mohammad Asghar (Oscar) AM Leighton Andrews Rebecca Evans Elin Jones Darren Millar Lynne Neagle Gwyn R Price Lindsay Whittle Kirsty Williams
Witnesses:	Kate Chamberlain, Healthcare Inspectorate Wales Mandy Collins, Health Inspectorate Wales Alyson Thomas, Healthcare Inspectorate Wales Emma Coles, Welsh Government David Pritchard, Welsh Government Mark Drakeford, Minister for Health and Social Services Grant Duncan, Welsh Government Janet Davies, Welsh Government
Committee Staff:	Llinos Madeley (Clerk)

Joanest Jackson (Legal Advisor)

1 Introductions, apologies and substitutions

1.1 There were apologies from Darren Millar AM. Mohammad Asghar AM substituted.

2 Inquiry into the work of Healthcare Inspectorate Wales: Evidence from Healthcare Inspectorate Wales

2.1 Representatives of the Healthcare Inspectorate Wales responded to questions from committee members.

2.2 The witnesses noted that they would welcome an opportunity to re-appear before the Committee when the Inspectorate's business plan for future years is available.

3 Factual briefing on the future of regulation and inspection of care and support in Wales White Paper

3.1 Members received a factual briefing from the Welsh Government on the *Future of Regulation and Inspection of Care and Support in Wales* White Paper.

4 Inquiry into the work of Healthcare Inspectorate Wales: Evidence from the Minister for Health and Social Services

4.1 The Committee scrutinised the Minister for Health and Social Services on the work of the Healthcare Inspectorate Wales.

4.2 The Minister agreed to write to the Committee to clarify whether the Inspectorate's work programme is signed off by one of his ministerial colleagues.

5 Papers to note

5.1 Letter from the Deputy Minister for Social Services: Revised Legislation Consent Memorandum on the Care Bill – reciprocal arrangements for local authorities in Scotland

5.1 The Committee noted the letter.

5.2 Letter from the Minister for Health and Social Services: follow-up information from the 9 October meeting on unscheduled care – preparedness for winter 2013/14

5.2 The Committee noted the letter.

5.3 Letter from the South Wales Plan Programme Board: further follow-up information from the 3 October meeting on local health board service reconfiguration

5.3 The Committee noted the letter.

6 Motion under Standing Order 17.42 to resolve to exclude the public from the remainder of the meeting and for agenda items 1 and 2 of the meeting on 13 November

6.1 The motion was agreed.

7 Consideration of the Committee's proposed inquiry into addiction to prescription and over the counter medicines

7.1 The Committee considered the proposed inquiry into addiction to prescription and over the counter medicines. Members agreed to postpone the start of the inquiry until work outlined in the *Working Together to Reduce Harm (Substance Misuse) Delivery Plan 2013-15* - scheduled for delivery by March 2014 - is completed.

8 Consideration of supplementary Legislative Consent Memorandum: Care Bill

8.1 The Committee considered the supplementary Legislative Consent Memorandum on the Care Bill and agreed to consider a draft report at its next meeting on 13 November 2013.

Health and Social Care Committee

Meeting Venue:	Committee Room 3 – Senedd
Meeting date:	Wednesday, 13 November 2013
Meeting time:	09:02 – 12:14

Cynulliad Cenedlaethol Cymru
National Assembly for Wales

This meeting can be viewed on Senedd TV at:
http://www.senedd.tv/archiveplayer.jsf?v=en_400000_13_11_2013&t=0&l=en

Concise Minutes:

Assembly Members:	David Rees (Chair) Leighton Andrews Rebecca Evans William Graham Elin Jones Darren Millar Lynne Neagle Gwyn R Price Lindsay Whittle Kirsty Williams
Witnesses:	Gwenda Thomas, Deputy Minister for Social Services Julie Rogers, Welsh Government Mike Lubienski, Welsh Government
Committee Staff:	Llinos Madeley (Clerk) Helen Finlayson (Second Clerk) Sarah Sargent (Deputy Clerk) Victoria Paris (Researcher) Joanest Jackson (Legal Advisor) Lisa Salkeld (Legal Advisor)

1 Consideration of the Legislative Consent Memorandum: Care Bill

1.1 The Committee discussed and agreed the draft Report on the Legislative Consent Memorandum relating to the Care Bill.
1.2 The Committee agreed to lay the Report in advance of the deadline set by Business Committee.

2 Discussion on the Forward Work Programme

2.1 The Committee agreed to undertake an inquiry into the availability of bariatric surgery in Wales and agreed terms of reference for the inquiry.
2.2 The Committee agreed to undertake a public consultation; details of which will be made available shortly.

3 Introductions, apologies and substitutions

3.1 No apologies were received.
3.2 The Chair welcomed the Deputy Minister for Social Services and her officials to the meeting.

4 Social Services and Well-being (Wales) Bill: Stage 2 - Consideration of amendments

4.1 In accordance with Standing Order 26.21, the Committee disposed of the following amendments to the Bill:

New Section:

Amendment 56A (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 56A was not agreed.		

Amendment 56 (Kirsty Williams)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0

As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 56 was not agreed.

Section 2:

Amendment 111 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees Kirsty Williams	0
4	6	0

Amendment 71 (William Graham) was agreed in accordance with Standing Order 17.34(i).

Amendment 72 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 71 was not agreed.		

Section 3:
No amendments were tabled to this section, therefore Section 3 was deemed agreed.

Section 4:

Amendment 64 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 64 was not agreed.		

Amendment 417 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 418 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 65 (William Graham)
As Amendment 418 was agreed, Amendment 65 fell.

Amendment 419 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 66 (William Graham) was agreed in accordance with Standing Order 17.34(i).

Amendment 420 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 421 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 57 (Kirsty Williams) was agreed in accordance with Standing Order 17.34(i).

Amendment 180 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 180 was not agreed.		

Section 5:

Amendment 422 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 67 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 67 was not agreed.		

Amendment 100 (Kirsty Williams)

For	Against	Abstain

Elin Jones Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans William Graham Darren Millar Lynne Neagle Gwyn Price David Rees	0
3	7	0
Amendment 100 was not agreed.		

Section 6:

Amendment 472 (Elin Jones)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 472 was not agreed.		

Amendment 84A (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 84 as amended (William Graham) was agreed in accordance with Standing Order 17.34(i).

Amendment 423 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 473 (Elin Jones)
As Amendment 472 was not agreed, Amendment 473 fell.

Amendment 68 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 68 was not agreed.		

Amendment 85 (William Graham)

For	Against	Abstain

Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 85 was not agreed.		

Amendment 86 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 86 was not agreed.		

Section 7:

Amendment 252 (William Graham)

For	Against	Abstain
William Graham Darren Millar Kirsty Williams	Leighton Andrews Rebecca Evans Elin Jones Lynne Neagle Gwyn Price David Rees Lindsay Whittle	0
3	7	0
Amendment 252 was not agreed.		

Amendment 289 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 88 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
4	5	0
Amendment 88 was not agreed.		

Section 8:

Amendment 73 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 73 was not agreed.		

Amendment 424 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 74 (William Graham)
As Amendment 73 was not agreed, Amendment 74 fell.

Section 9:

Amendment 4 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 5 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 6 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 474 (Elin Jones) was not moved.

Amendment 7 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

New Section:

Amendment 475 (Elin Jones)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 475 was not agreed.		

Amendment 476 (Elin Jones)
As Amendment 475 was not agreed, Amendment 476 fell.

Section 10:

Amendment 234 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 234 was not agreed.		

Amendment 235 (William Graham)
As Amendment 234 was not agreed, Amendment 235 fell.

Amendment 89 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees Kirsty Williams	0
4	6	0
Amendment 89 was not agreed.		

Amendment 236 (William Graham)
As Amendment 234 was not agreed, Amendment 236 fell.

Amendment 8 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 9 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 237 (William Graham)
As Amendment 234 was not agreed, Amendment 237 fell.

Amendment 90 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees Kirsty Williams	0
4	6	0
Amendment 90 was not agreed.		

Amendment 87 (William Graham)

For	Against	Abstain

Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 87 was not agreed.		

Amendment 10 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 11A (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 11A was not agreed.		

Amendment 11 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 115 (Kirsty Williams)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 115 was not agreed.		

Section 11:
No amendments were tabled to this section, therefore Section 11 was deemed agreed.

Section 12:

Amendment 116 (Kirsty Williams) was not moved.

Amendment 91 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price	0

	David Rees Kirsty Williams	
4	6	0
Amendment 91 was not agreed.		

Amendment 12 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 13 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 14 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 15 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 117 (Kirsty Williams)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 117 was not agreed.		

Amendment 290 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Section 13:
No amendments were tabled to this section, therefore Section 13 was deemed agreed.

Section 14:

Amendment 112 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 112 was not agreed.		

Amendment 16 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Section 15:

Amendment 238 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 238 was not agreed.		

Amendment 17 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 239 (William Graham)
As Amendment 238 was not agreed, Amendment 239 fell.

Amendment 240 (William Graham)
As Amendment 238 was not agreed, Amendment 240 fell.

Amendment 241 (William Graham)
As Amendment 238 was not agreed, Amendment 241 fell.

Amendment 92 (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees Kirsty Williams	0
4	6	0
Amendment 91 was not agreed.		

Amendment 18 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 19 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 20 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 21A (William Graham)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price	0

Kirsty Williams	David Rees	
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 21A was not agreed.		

Amendment 21 (Gwenda Thomas) was agreed in accordance with Standing Order 17.34(i).

Amendment 118 (Kirsty Williams)

For	Against	Abstain
Elin Jones William Graham Darren Millar Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans Lynne Neagle Gwyn Price David Rees	0
5	5	0
As there was a tied vote, the Chair's casting vote was applied in the negative, in accordance with Standing Order 6.20(ii). Therefore, Amendment 118 was not agreed.		

Section 16:
No amendments were tabled to this section, therefore Section 16 was deemed agreed.

Section 17:

Amendment 248 (William Graham) was not moved.

Amendment 249 (William Graham)
As Amendment 248 was not moved, Amendment 249 fell.

New Section:

Amendment 477 (Elin Jones)

For	Against	Abstain
Elin Jones Lindsay Whittle Kirsty Williams	Leighton Andrews Rebecca Evans William Graham Darren Millar Lynne Neagle Gwyn Price David Rees	0
3	7	0
Amendment 477 was not agreed.		

4.2 Sections 2 to 17 were deemed agreed.

5 Papers to note

5.1 The Committee noted the letters from the Minister for Health and Social Services and Deputy Minister for Social Services.

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Welsh Stroke Alliance
c/o Dr Anne Freeman
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Pencoed
CF35 5LJ

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 achieve 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.*

[2] Additional evidence to the NAfW follow up inquiry into stroke risk reduction. 2013.

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 stroke[5].

2) Economic Burden

A number of studies have estimated the percentage amount of health care expenditure spent on direct stroke care around the world[67]. 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:

• Prevention with interventions that reduce hypertension • Prevention in patients with atrial fibrillation • Prevention using statins • Prevention through smoking cessation	• 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

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.

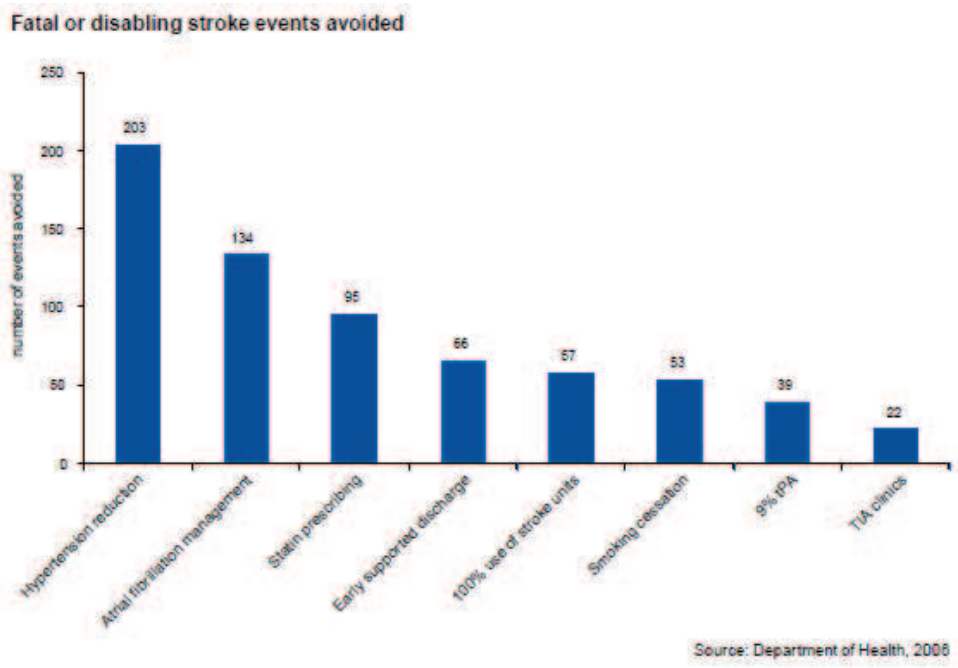

Chart 1: Number of fatal or disabling stroke events avoided

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

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Cymru Wales National Office
General Practitioners Committee (Wales)

David Rees AM
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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,

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

John Gallacher, BSc, PhD, Anthony Bayer, MB BCh, Mark Fish, MB BCh, Janet Pickering, BSc, MSc, Sofia Pedro, BSc, MSc, Frank Dunstan, MA, PhD, Shah Ebrahim, MB BCh, MD, and Yoav Ben-Shlomo, MB BCh, PhD

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 ($b_{age\ adj} = -0.291$ (-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 findings 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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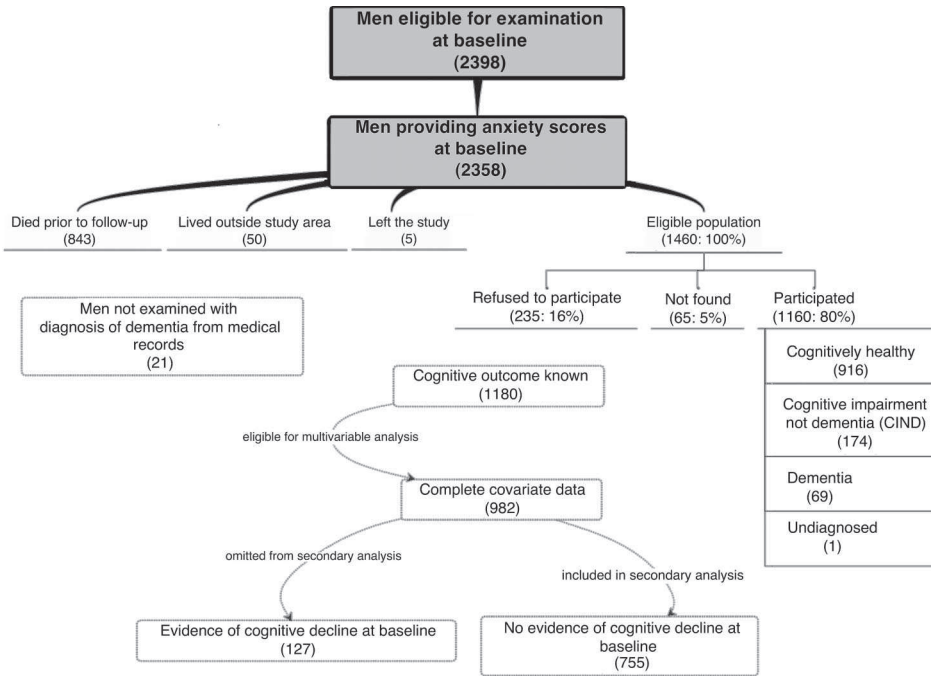

Figure 1. Cohort recruitment.

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 amnestic 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. Preliminary 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+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

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

Covariates	Men in Follow-Up				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	All (n = 1160)		
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.

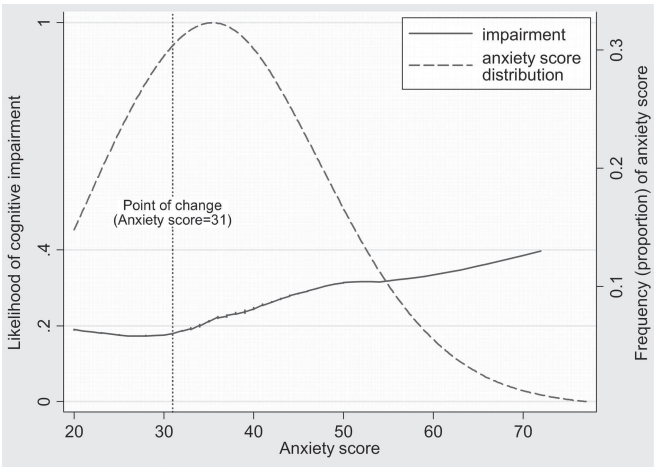

Figure 2. Lowess smoothing of cognitive impairment according to Anxiety score in 1160 men who were cognitively screened.

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 E_4 (high risk), heterozygous E_4 (moderate risk), and non-E_4 (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 (χ^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, *p*				
		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
	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
	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
	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 ($OR_{age\ ajd} = 5.04$; 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) ($b_{age\ adj} = -0.291$; 95% CI = −0.551, −0.032; $p =$ .028) and praxis ($b_{age\ adj} =$ −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

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

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 depression 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.

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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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Is Sticky Blood Bad for the Brain?

Hemostatic and Inflammatory Systems and Dementia in the Caerphilly Prospective Study

John Gallacher, Antony Bayer, Gordon Lowe, Mark Fish, Janet Pickering, Sofia Pedro, Frank Dunstan, James White, John Yarnell, Yoav Ben-Shlomo

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 specific 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

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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 α2-macroglobulin and α1-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 (Frag1+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 examination[13]; the Rosen-Modified Hachinski Ischaemic Score (HIS)[14]; the Frontal Assessment Battery[15]; 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 AD[19] 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,

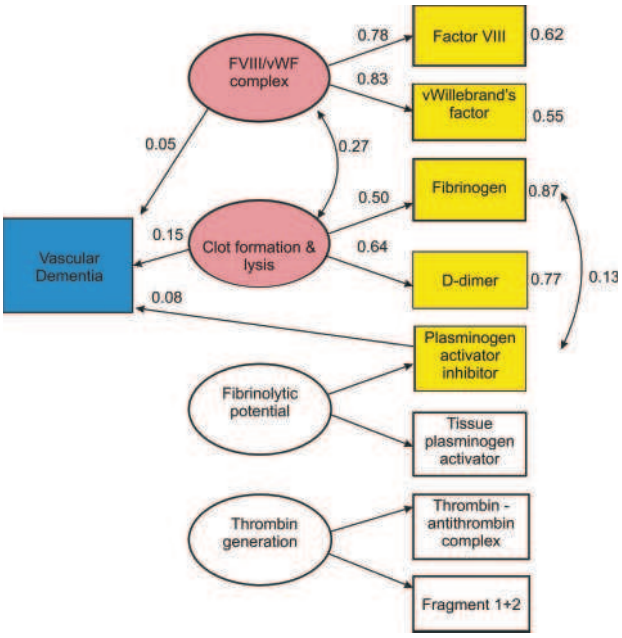

Figure. Structural equation modeling analysis of hemostatic pathways.

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 α2-macroglobulin (mean, 15.7 g/100 g vs 15.2 g/100g; $P=0.03$) and α1-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 α2-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*

	Vascular Impairment (n=53)		Non Vascular Impairment (n=133)		Vascular Dementia (n=27)		Non Vascular Dementia (n=26)	
Type of Marker	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, χ^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 (β=.05, P<0.05) and clot formation and lysis (β=.15, P<0.05) were associated with vascular dementia. The observed variable PAI-1 was also independently associated with vascular dementia (β=.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

	Latent Variable			
Hemostatic Marker	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 premorbid 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 function[26] 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.

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Disclosures

None.

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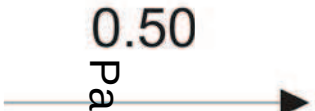
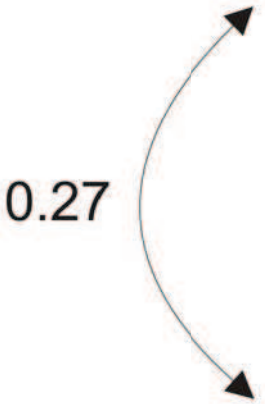
Observed variables (haemostatic markers and dementia)

Latent variables (haemostatic pathways: from factor analysis)



Standardised path (regression) coefficient fromindependent to dependent variable



Standardised covariance between independent variables: double headed arrow

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/

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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.

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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.

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 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 anxiety[16] 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

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 Rating[22] 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 neuroimaging 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 dementia[25] 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: 103 men taking benzodiazepines at any phase	Use of benzodiazepines: 1085 men never used benzodiazepines	Difference (95% CI)	p Value
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.

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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 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.

GIG CYMRU NHS WALES
Bwrdd Iechyd Aneurin Bevan Health Board

Ref: JS/LM/sm Direct Line: 01633 435933 11 November 2013

FAO Llinos Madeley, Committee Clerk
Health and Social Care Committee
National Assembly for Wales
Cardiff Bay
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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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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

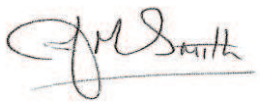
The core annual funding for the South Wales Cancer Network, agreed in 2011/12 by the Welsh Assembly Government, is £368,000 pa.

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
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Mark Drakeford AC / AM
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Minister for Health and Social Services

Llywodraeth Cymru
Welsh Government

Ein cyf/Our ref: SF/MD/3618/13

David Rees AM
Chair
Health and Social Care Committee
National Assembly for Wales
Cardiff Bay

11 November 2013

Dear David

Thank you for your letter dated 30 September 2013 requesting an update on provision of services by the Children's Immunisation Centre in Wales.

Health Inspectorate Wales (HIW) has been in contact with the Children's Immunisation Centre (CIC) and the company has indicated hat it has no plans at this time to provide its services in Wales again. HIW has advised CIC that if the company did decide to deliver vaccination services in Wales in the future, the company would need to contact HIW before it did so.

HIW is continuing to work with Legal Services with the aim of closing the existing legal loophole that allows such "one-off" clinics to practice in Wales without being registered. This work is expected to be completed before Christmas this year. I will provide the Committee with a further update when options have been considered.

Best wishes

Mark

Mark Drakeford AC / AM
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Ein cyf/Our ref: MB/MD/5089/13

David Rees AM
Chair
Health and Social Care Committee

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11 November 2013

Dear David,

Health Boards and Welsh Ambulance Services NHS Trust (WAST) Unscheduled Care and Winter Plans

Further to my letter of 31st October 2013 please find the attached table which provides links to published Unscheduled Care and Winter Plans, and indicates when other Health Boards and WAST intend to publish their plans.

Best wishes

Mark

Mark Drakeford AC/AM
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Unscheduled Care and Winter Plans - Publishing Progress and Links to Published Plans

Health Board Area	Published USC Plan	Published Winter Plan
Cwm Taf	**Published at:** http://www.wales.nhs.uk/sitesplus/865/page/49128	**Published at:** http://www.wales.nhs.uk/sitesplus/865/page/49128
Betsi Cadwaladr	**Published at:** http://www.wales.nhs.uk/sitesplus/documents/861/13_119_3%20Urgent%20and%20Emergency%20Care%20Strategy%20NW%202013_2016%20amended%20p6.pdf	**Due to be published: 28 November**
Aneurin Bevan	**Published at:** http://www.wales.nhs.uk/sitesplus/866/news/29656	**Due to be published: 27 November**
ABMU	**Due to be published: 14 November**	**Due to be published: 14 November**
Cardiff & Vale	**Due to be published: by end of November**	**Due to be published: by end of November**
Hywel Dda	**Due to be published: 21 November**	**Due to be published: 21 November**
Powys	**Published Draft at:** http://www.wales.nhs.uk/sitesplus/867/page/70221 **Final versions due to be published: December**	**Published Draft at:** http://www.wales.nhs.uk/sitesplus/867/page/70221 **Final versions due to be published: December**
WAST	**Due to be published: by end of November**	**Due to be published: by end of November**

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